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Section of Surgery

SUB-SECTION OF PROCTOLOGY

President—W. ERNEST MILES, F.R.C.S.

[*November* 14, 1934]

Melanosis Coli.—CUTHBERT DUKES, M.D.

In the condition known as melanosis coli, or pigmented colon, the mucous membrane of the colon and rectum appears darker than usual, the depth of colour varying from pale grey to brown or black. This is due to the deposition in the mucous membrane of a pigment closely allied to melanin. This pigment is formed from protein-degradation products absorbed from the intestine, these being converted into melanin by ferments within the connective tissue cells. As a rule, the colour is deepest in the region of the cæcum and ascending colon. It begins abruptly at the ileocæcal valve, and in the pelvic colon and rectum fades off by degrees. When the surface of a pigmented colon is examined with a lens the distribution of the pigment is seen to be uneven. The dark areas are hedged round by tiny colourless lines which correspond to the ramifications of the mucosal blood-vessels. Microscopic examination shows the pigment lying within the cytoplasm of large mononuclear cells which are scattered through the stroma of the mucous membrane. The glandular epithelium itself is free from pigment. The submucosa may contain a few pigmented cells, and in severe degrees of melanosis there may be metastatic pigment granules within the mesocolic glands, colouring them brown.

In its milder forms melanosis coli is not a rare condition, but the figures given for its incidence vary with different writers, according to the standards adopted. In Stewart and Hickman's [1] series of 600 autopsy cases in which they closely scrutinized the colon, 67 cases of melanosis coli were detected—an incidence of 11·2%. The more extreme grades of pigmentation, however, are comparatively rare, and are met with only in later life.

Although the pigmentation is not in any way detrimental to health, it is to be regarded as evidence of disordered function. Clinical experience suggests that pigmentation is dependent on previous intestinal stasis. In keeping with this, we find that melanosis is commoner in cases of cancer of the colon than in non-cancer cases, and moreover, in instances of melanosis associated with tumours of the colon, the pigmentation is always more conspicuous above, than below, the obstructing growth.

Individuals affected by melanosis coli are, of course, unaware of their peculiarity, no other organs of the body being affected. The subject has very little practical importance but is of considerable academic interest in relation to melanin pigmentation in animals and in other organs in man. For instance, the ink-sac of the cuttle-fish is lined by cells capable of producing enormous quantities of melanin, and when danger is threatened the fish suddenly swims backward, expelling a cloud of black fluid from its ink-sac [2]. In the skin of the chameleon there is a mechanism for the quick transport of melanin pigment, thus altering the colour according to the surroundings. Melanin pigmentation is of interest in human pathology because of those diseases in which it causes severe disfigurement. In Addison's disease, owing to destruction of the suprarenals, adrenalin can no longer be formed, so the mother-substance of adrenalin is converted into melanin instead, resulting in the characteristic pigmentation of the skin. The distressing condition known as ochronosis, the

victims of which develop a yellow-ochre colour in the nose and ears, is due to deposits of melanin in the cartilages and connective tissues. Finally, in melanotic tumours melanin may be produced in prodigious quantities. The entire skin of the human body does not contain more than one gram of melanin pigment, but in the secondary deposits of a melanotic carcinoma more than 300 grams of melanin have been removed from the liver. Another instance of nature's prodigality in melanin is seen in tumours of horses. Pigmented tumours are very common in white or grey horses but rare in dark horses. It is said that if a white horse lives long enough it is almost certain to die of melanoma, and so great is the amount of melanin found that farmers have considered using the pigment as paint for their fences.

The pigmentation of melanosis coli, though not on such a lavish scale, is sufficient to cause astonishment when present to such a degree as is shown by the three cases I am exhibiting to-day. These are all cases of cancer of the rectum in patients affected by melanosis coli. One of these shows a very deep, almost black, pigmentation of the mucous membrane. In the other two the pigmentation is a lighter brown shade. There is no pigment in the malignant tumours or in associated adenomatous growths, so that those appear as light areas on a dark background.

[1] *Journ. Path. and Bact.*, 1931, xxxiv, No. 1, 61-73.
[2] *Brit. Med. Journ.*, 1923 (ii), 907-911.

Professor M. J. STEWART said that he could confirm Dr. Dukes' observation that adenomatous polypi occurring in a colon which was the seat of melanosis failed to show pigmentation, at least when they were of recent formation. Metastasis of melanin to the regional lymph-glands, by means of large mononuclear phagocytes, was of frequent occurrence in the more advanced cases. In this connexion it was worth recalling to mind that similar metastasis of phagocyted melanin might take place from malignant melanomatous tumours, even apart from genuine neoplastic metastasis. The blue or black appearance of the mucous membrane in the more extreme examples of melanosis coli was due to the layer of mucus on the surface. If this was wiped away, the rich, deep mahogany-brown tint, the normal colour of the melanin, was exposed to view.

Perineo-abdominal Excision of the Rectum in one Stage.—W. B. GABRIEL, M.S.

Our President [1] described his abdomino-perineal excision of the rectum, in 1908, and it has gained wide-world recognition as being the most radical operation that can be done for cancer of the rectum. After an interval of a few years, various modifications, designed to reduce the immediate mortality, began to be introduced; in 1915 Coffey [2] and D. F. Jones [3] described their two-stage methods; in 1921 Graeme Anderson [4] described before this Sub-Section a three-stage abdomino-perineal excision; and in 1928-29 Dudley Smith [5] and Rankin [6] described two-stage operations in which the abdominal part of the operation was completed first and the rectal stump removed after an interval of from ten to fourteen days. There are definite objections to these methods and they have never, I believe, been widely adopted in this country.

Grey Turner [7] in 1920 reported seven cases of perineo-abdominal excision of the rectum as a second-stage operation after a preliminary colostomy. I have performed fourteen operations of this type and have six patients alive and well for two and a half to six years after operation, but there occurred in this series five deaths (35%), of which four were from sepsis (peritonitis or wound sepsis).

The operation is the outcome of my experience with these methods: it is a combined excision in one stage beginning from the perineum, and was described by me in the *Lancet* last July [8]. It is divided into four well-defined stages[1]:—

(1) A preliminary laparotomy to confirm operability, with temporary suture of the wound.

[1] These were illustrated by a film.

(2) The perineal stage, the first part of which is carried out strictly according to Lockhart-Mummery's technique for perineal excision. The peritoneum is then opened widely from below, the lateral ligaments are divided, and the mobilized rectum, enveloped in flavine or dettol gauze with a glove tied tightly round, is pushed up into the pelvis. There is no interference with the superior hæmorrhoidal pedicle from below.

(3) The abdominal incision is reopened and the rectum is delivered upwards. The inferior mesenteric pedicle is doubly ligated and divided. A left iliac incision is made, and the space lateral to the iliac colon is closed by suture; the rectum and pelvic colon are delivered outwards through this incision up to the stitch closing the lateral space. The pelvic floor is sutured, and both abdominal incisions are closed and packed off. The bowel is divided with a cautery between clamps and a No. 17 rubber catheter is passed down the bowel and sutured in.

(4) Finally the legs are held up and the toilet of the perineal wound is completed. Usually I have put in a sterilized rubber bag and packed it with gauze; recently I have inserted only a corner of gauze, and have allowed the soft parts to fall in from the outset. I believe this latter plan may be preferable and result in quicker healing.

In certain selected cases (16 out of 35), I have dispensed with the preliminary exploration, and have performed the operation as a blind excision from below; with experience in assessing operability I think this is a safe and sound procedure. In my present total of 35 perineo-abdominal excisions in one stage there have been seven deaths (20%), but I am confident that the mortality should now be reduced to the neighbourhood of 10%.

Provided the operator has graduated in what I may call the "perineal excision school"—or is willing to learn the rather difficult technique of perineal excision—he can confidently set out to perform this operation. I find the perineo-abdominal excision easier than the operation which we have all seen Mr. Miles carry out in his inimitable fashion; the extra-abdominal division of the colon renders the risk of septic complications very remote, and I believe that, by this new operation, the range of combined excision of the rectum will be extended so that subjects, hitherto considered unsuitable, will come safely through this radical operation. In particular, the operation can be carried out with relative ease in stout subjects, and I have put out for inspection three long specimens each showing a fat-laden rectum and pelvic colon, which I have recently excised from fat subjects (females aged 40, 57 and 64 respectively); recovery has followed in each case, and one patient, aged 64, is due to leave hospital in a few days' time—twenty-six days after the operation. So far as age is concerned, my limit at present is a man aged 77 at the date of operation who is now alive and well—eighteen months later.

Except for the case of the solitary small carcinoma low down in the rectum, I agree with Mr. Miles in his advocacy of the combined operation. Nearly 70% of rectal carcinomas occur in the upper third of the rectum, and metastases in the glands occur in about 50% of operation cases; on these grounds alone a combined excision is indicated in the majority of cases. Since the beginning of 1932 my allocation of operation in 53 cases has been as follows: perineo-abdominal 35, perineal excision 17, conservative resection one.

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Hydatid Cyst of the Rectum.—P. LOCKHART-MUMMERY, F.R.C.S.

W. E., a man aged 59, was operated on for hydatid cysts of the liver twenty-eight years ago, and a number of cysts were removed, together with a large portion of the liver.

He came into St. Mark's Hospital in April 1934 complaining of stoppage of the bowels, with pain in the rectum and back, for the last two months, and occasional bleeding for a year.

On examination.—A hard mass was discovered in the rectovesical pouch Bimanually this was found to be not in the rectum itself, but in the tissues between the rectum and bladder, and it was slightly movable. The rectum was considerably obstructed. Sigmoidoscope examination showed that there was no lesion in the bowel itself.

There was a second large, oblong swelling in the lower part of the scar in the abdominal wall in the right hypochondrium (fig. 1). This had been previously

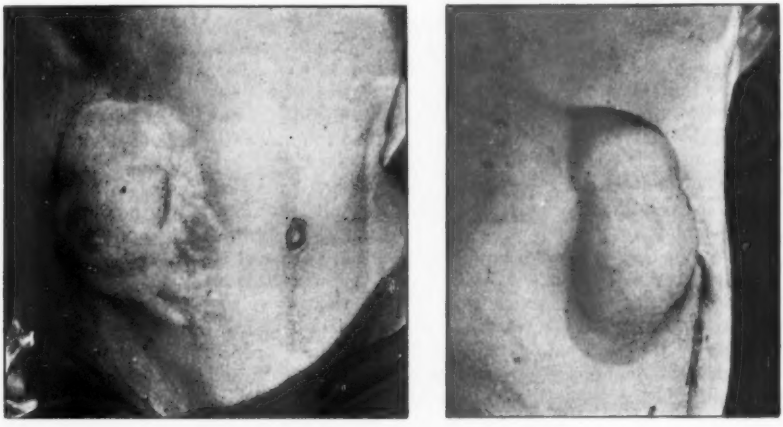


FIG. 1.—Hydatid cyst of the abdominal wall.

diagnosed as a ventral hernia, but was evidently a cyst in the scar, projecting both into the abdomen and under the skin.

X-ray examination showed nothing except a suggestion of a calculus in the lower part of the right kidney.

The blood-count was normal and there was no eosinophilia.

In view of the patient's history and of the cyst in the right side of the abdomen, a diagnosis was made of echinococcus cyst, and it was believed that the mass felt in front of the rectum was also an echinococcus cyst.

Operation was performed in May 1934. When the abdomen was opened a large cyst could be seen lying between the bladder and the rectum. With a little dissection this was shelled out from the tissues and came out complete. The bed from which the cyst was removed was easily restored by drawing peritoneum into the gap. The other cyst in the abdominal wall was then also removed, and behind it a third cyst, about the size of a golf-ball, was discovered. This was also removed. No other cysts were found anywhere in the abdomen.

The gap in the abdominal wall where the cyst had been was restored by drawing the muscles and aponeurosis together, and the abdomen was closed.

The patient made a very good recovery and when examined in June and July 1934 was found to be quite well.

Description of the specimen.—The cyst removed from the rectum had calcified walls (fig. 2) and contained live scolices and hooklets. The second cyst, removed from

FIG. 2.—Calcified hydatid cyst of the rectum, cut in half.

the abdominal wall, was degenerated and the contents were dead and consisted of brown pultaceous material of the third cyst was similar. The only active cyst, therefore, was the one in the rectum.

The interest of the case lies in the extreme rarity of hydatid cysts involving the rectum, and in the fact that a correct diagnosis was made before operation.

Fibrous Stricture of the Rectum.—P. LOCKHART-MUMMERY, F.R.C.S.

The patient, a married woman, aged 40, was admitted into St. Mark's Hospital in February 1923. The condition had resulted apparently from a bad confinement complicated by placenta prævia. She was having diarrhœa four or five times a day.

On examination there was a hard, indurated stricture 3 in. from the anus, and about 2 in. in length. It was very tight and would not admit a finger. The strictured part of the bowel was movable and there was no bad ulceration. The walls were extremely thick, and it was obvious that dilatation was impossible and the stricture was too high for proctotomy.

A temporary transverse colostomy was performed, and a fortnight later the rectum was cut down upon from behind—after removal of the coccyx—and mobilized. About 4 in. of the rectum was then excised by dividing it across, above the anal canal, and about 2 in. above the stricture. A 1-in. diameter tube was passed through the anus and into the colon, and the end of the colon was stitched end-to-end to the stump of the rectum. The posterior wound was closed with a cigarette drain. On April 14 a No. 24 bougie was passed quite easily and the patient was discharged.

In May 1923 the patient returned. The colostomy was closed intraperitoneally and a temporary cæcostomy was performed. The cæcostomy tube was removed ten days later.

On October 16, 1923, the patient was examined again. The site of the stricture was found to be firmly healed, and a No. 22 dilator was passed quite easily. The patient has not been seen since.

The specimen shows a dense fibrous stricture involving about 2 in. of the rectum, with thick walls and hypertrophy of the rectal wall above.

The ætiology of the stricture is not quite clear, but it seems probable that it was due to ordinary chronic sepsis following a confinement.

Fistula-in-ano arising from an Intramuscular Gland.—Sir CHARLES GORDON-WATSON, K.B.E., F.R.C.S.

The patient, a man, aged 36, began to have trouble with piles six months ago. Four months ago he first noticed some yellowish discharge from the anus. Recently he has had some pain and tenderness at the anal margin.

On rectal examination a small peri-anal swelling, about the size of a pea, was detected at the anal margin anteriorly. The swelling was firm and appeared to be in the substance of the sphincter.

On examination of the anal canal a small fistulous track about half an inch long was detected leading directly into the swelling.

At operation (18.6.34) a probe was passed into the abscess cavity, the cavity was dissected out intact from the substance of the external sphincter, and a radical operation for direct fistula was carried out. Hæmorrhoids were also ligatured. Recovery was straightforward.

Pathological report (Cuthbert Dukes).—Tissue from anal region: "The fragment consists of sphincter muscle and connective tissue from the anal region. A small abscess is situated between the fibres of the sphincter muscle, and in contact with this is the duct of a gland lined by transitional epithelium. This duct has the histology of an intramuscular gland arising from the anal canal, and the appearances suggest that the abscess is related to the presence of the gland."

I reported a similar case to the Sub-Section in January 1932,[1] and another will be recorded by Mr. Harold Dodd.

The accounts of these three cases have been embodied in a paper illustrating the relationship between peri-anal glands and fistula-in-ano which is to appear in the *British Journal of Surgery*.

Pedunculated Rectal Polypus, showing Malignant Change.—Sir CHARLES GORDON-WATSON, K.B.E., F.R.C.S.

The polypus was removed by ligature of the stalk, from a man, aged 50, who complained of a lump coming down during defæcation. No other polypus or adenomata were found in the rectum.

Pathological report (Cuthbert Dukes).—"An adenoma which has commenced to undergo malignant change. At each edge the growth has the histology of a benign adenoma, but in the centre the glandular epithelium is arranged in a very irregular fashion, and has commenced to invade the submucosa. In this region there are many atypical mitotic figures.

I have previously reported to the Sub-Section a somewhat similar case. In that instance the malignant adenoma was not pedunculated and the base of the tumour was three-quarters of an inch wide. The tumour was removed with a half-inch free margin of mucosa and the edges were sutured. After the pathological report of early malignant change was received radium needles were embedded

[1] *Proceedings*, 1932, xxv, 1019.

behind the tumour area through the posterior vaginal wall. At the end of eighteen months there was a recurrence. The patient was a victim of congenital telangiectasis in the nose and suffered from frequent and severe hæmorrhages. She was considered unfit for radical surgery, and the recurrence has been treated by interstitial radiation with radon. Although there has been some retrogression the condition has not been cured and a second application of radon has been carried out three months after the first.

These two cases presented difficult problems as to the right course to pursue. Obviously a pedunculated malignant adenoma is a less serious menace than a sessile one. The subsequent history of the case in which the growth was sessile showed the danger of relying on a minor local removal. Yet in this type of case an exact diagnosis cannot be made before removal. A biopsy is obviously unreliable, because the area of malignant change is so small. I wonder whether members think that a conservative resection of the rectum should have been carried out after the pathological report had been received. I do not propose to do anything further in the case of the pedunculated growth, except keep a careful watch. The danger in this type of case is that the rectal mucosa is potentially malignant, and adenomata may arise elsewhere in the rectum and become malignant.

Specimen of Carcinoma of Recto-Sigmoidal Region treated by Hartman's Operation.—LIONEL NORBURY, F.R.C.S.

Mrs. F., aged 62. History of loose motions for four months. Slight loss of weight.

Digital examination revealed a mass just above the level of the cervix uteri.

Sigmoidoscopy showed growth at 15 cm. Portions removed for microscopy by Bruning's forceps and reported as "adenocarcinoma."

Abdominal exploration, August 1934. — Growth just above rectosigmoidal junction. A large mass of uterine fibroids and also a left-sided ovarian cyst complicated full exposure.

Operation.—Subtotal hysterectomy and removal of an ovarian cyst were followed by division of the bowel below the growth, removal of the pelvic colon and formation of a terminal colostomy. The divided end of the rectum was closed by suture. The patient made a good recovery.

The growth had spread into the extracolic tissues. The regional lymph-nodes did not contain metastases—in other words, this was a B case.

Specimen of Rectum and Colon from a Case of Fæcal Impaction in a Girl aged 18.—LIONEL NORBURY, F.R.C.S.

E. C., aged 18, mentally defective. Admitted to Royal Free Hospital, October 1932, on account of fæcal accumulation.

Had an operation for imperforate anus with recto-vaginal fistula, when a baby.

A hard fæcal mass arose out of the pelvis to the level of the umbilicus.

Examination under anæsthetic.—Stenosed anal canal stretched; fæcal mass broken up digitally and bowel subsequently cleared.

August 30, 1934: Readmitted on account of fæcal accumulation. Abdomen greatly distended; hard mass filling right iliac region. Rectum tightly packed with fæces; anal canal narrow.

October 9, 1934: Under general anæsthesia, the fæcal mass was broken up as much as possible, after stretching of the anal canal. Copious enemata were given. The abdomen remained distended, and there were only poor results from the enemata. Vomiting began fifteen days after the anæsthetic and became fæcal in type. The patient became cyanosed and died.

Post-mortem findings.—Abdomen much distended. A few ounces of slightly turbid fluid in peritoneal cavity. Stomach dilated; contained fæcal matter.

Small bowel much dilated, hypertrophied and congested. Large bowel enormously dilated and hypertrophied (rectum 9 in. in diameter, colon 5 in.) and contained hard fæcal masses. Anus represented by a fibrous ring; admitted one finger. Vagina small; no communication with rectum.

Thoracic contents pushed up and compressed by diaphragm which rose high into thorax.

Bilateral hydronephrosis and hydro-ureter. No other congenital abnormality.

Supposed cause of death: Asphyxia and syncope.

Specimen of Tuberculous Stricture of Small Intestine.—LIONEL E. C. NORBURY, F.R.C.S.

S. E., female, aged 50 years, admitted to the Royal Free Hospital, August 27, 1934.

Four months' history of abdominal pain with acute exacerbations, associated with vomiting and constipation.

Abdomen distended—"splashing" elicited all over abdomen. No visible peristalsis.

Barium meal showed dilated coils of jejunum and proximal ileum. "Fluid levels" well shown.

Barium enema showed no abnormality of colon.

Exploratory laparotomy.—Tight annular stricture found in upper portion of small intestine. Bowel much dilated and hypertrophied above the lesion, but collapsed below it. Stricture resembled an "annular carcinoma." No other ulcers detected.

Resection of affected portion with lateral anastomosis.

Microscopical report.—"Tuberculous." Uneventful recovery.

Specimen of Tuberculous Ulceration of Cæcum with Large Stercolith.—LIONEL E. C. NORBURY, F.R.C.S.

The patient showed symptoms of chronic intestinal obstruction, associated with a palpable mass in the right iliac region, giving clinical features of carcinoma of the cæcum.

Operation revealed a hard contracted cæcum with a chain of small glands in the mesocolon. Condition regarded as carcinoma.

Treatment.—Resection and lateral anastomosis.

Examination of specimen.—Scarred and contracted condition of cæcum with large stercolith in a pouch connected with the lumen of the bowel. Report on microscopical examination: "Tuberculous."

Skiagram of Colon showing Result Two Years after Resection of Sigmoid for Carcinoma followed by End-to-End Anastomosis.—LIONEL E. C. NORBURY, F.R.C.S.

A preliminary transverse colostomy had been established on account of acute intestinal obstruction. This was subsequently closed by means of an enterotome.

The interest of the skiagram, taken after a barium enema, lies in the fact that very little, if any, abnormality of the colon can be detected.

Specimen of an Advanced Adenocarcinoma of the Rectum treated with Radium followed by Diathermy Perineal Excision.—C. NAUNTON MORGAN, F.R.C.S.

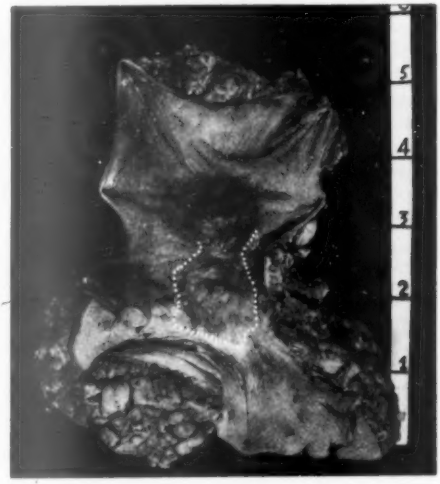
This specimen was obtained from a woman, aged 62, who attended St. Mark's Hospital in July 1933, with a carcinoma in the lower third of the rectum and anal canal. The growth was situated on the left side of the rectum and involved two-thirds of its circumference. It had extended deeply into the left ischiorectal fossa,

which was fixed firmly to the side of the anal canal and rectum. There were enlarged hard glands in the left inguinal region.

August 14, 1933: Exploratory laparotomy was performed through the rectus muscle and transposition of the viscera was discovered. There were no enlarged glands in the mesorectum or mesocolon and there were no glands felt along either the internal or external iliac vessels. The liver was free from growth. Colostomy was performed.

August 28, 1933: The growth was treated with interstitial radium. 4 needles of one mgm. were introduced into the growth intrarectally. 5 needles of two mgm. were inserted into the growth through the peri-anal and peri-rectal tissues. 4 needles of three mgm. and 1 needle of two mgm. were inserted into the ischiorectal fossa at the edge of the infiltrating growth.

These needles were filtered with 5 mm. of platinum and were left in for seven days. Thus the dose to the growth was 4,704 mgm. hours. The glands in the



Photograph of the excised rectum. The original area of growth is indicated by an interrupted line.

left groin were similarly treated by insertion of 6 needles of one mgm. for one week, the dose being 1,008 mgm. hours.

One month after operation the growth was found to be flat and smooth, there being a slight projection at its upper limit.

January 1934: Five months after the insertion of radium there was no obvious infiltration of the ischiorectal fossa. Rectal examination revealed a smooth induration at the site of the growth and the upper edge of this flat indurated area, a typical carcinomatous edge, could be felt.

March 1934: A block dissection of the glands in the left groin was carried out and adenocarcinomatous metastases were found in two of the seven glands examined. Five weeks after this operation the patient developed a spreading streptococcal infection from the incision in the left groin. The patient had a very stormy convalescence but finally recovered from the severe toxæmia.

August 1934: Three months after her last admission she was readmitted, and a diathermy perineal excision was carried out below the peritoneal

reflexion, which was gently stripped upwards. The contents of the ischiorectal fossæ were widely removed. The wound healed rapidly and well.

Pathological reports.—6.9.33 : This is a fragment of an adenocarcinoma.

7.9.33 : This is a fragment of an adenocarcinoma.

14.3.34 : The specimen consisted of a mass of glands from the groin. Seven separate lymph-nodes were dissected out and sectioned. Adenocarcinomatous metastases were present in two of the seven glands.

18.9.34 : The specimen measured 6 in. in length. A flat ulcerated growth, 1 in. in diameter, extended one-third round the lower third of the rectum, being situated on the anterior quadrant. Its lower edge reached down to the ano-rectal line, and there was 1½ in. free margin above. No papillomata were present.

Microscopical structure.—The tumour is an adenocarcinoma. Histological malignancy, Grade No. 2. A gland removed from the vicinity of the growth was free from carcinoma. The tissue sent separately from operation is infiltrated with carcinoma. From the point of view of prognosis, this is a C2 case.

I am reporting this case for the following reasons :—

(1) An inoperable carcinoma of the lower third of the rectum, owing to the pain and discomfort produced by infiltration of the anus, should be removed in order to make the patient comfortable.

(2) These low growths are accessible for accurate irradiation, and radium should be employed in inoperable cases.

(3) The cutting diathermy is a very valuable method.

(4) Radium will occasionally make a locally inoperable growth operable.

(5) The profound toxæmia of the erysipelas might take a part in preventing recurrence.

Section of Otology

President—E. A. PETERS, F.R.C.S.

[*November* 2, 1934]

Infections of the Eustachian Tube and Pulmonary Tract

PRESIDENT'S ADDRESS

By E. A. PETERS, F.R.C.S.

I PROPOSE to compare the respective methods of infection in the Eustachian tube with that of the pulmonary tract, which, after the protection of the regulating valve of the glottis, opens into open and almost fixed tubes, and then into the bronchioles, which contract or dilate and regulate the admission of air into the alveoli where the limit of pressure is 0·19 mm.

The Eustachian tube is a diverticulum of the first cleft. It commences as a cartilaginous tube, in which the walls are in contact, exercising control of the entry of air and exit of mucus. Swallowing opens the tube.

With an open lumen the outer two-thirds passes through a bony canal, and expands into the middle-ear cavity—the antrum and pneumatic mastoid cells.

The upper respiratory tract and its sinuses are lined by ciliated epithelium from the anterior margin of the middle turbinal to the palate level. The bucco-pharynx containing the lower half of Waldeyer's ring is covered by stratified epithelium and is scavenged by either swallowing or screeding.

Septic processes, whether acute or chronic, set up by organisms introduced with respired air, result in a rhinopharyngitis. Worms and Le Mee say that the tonsils share with the mucous membrane the early incidence of infection, which subsequently extends to the lungs; in acute cases infection of the rhinopharynx and lungs may be co-temporary. Chevalier Jackson has said that chronic sinusitis and septic tonsils stand in a causal relationship to bronchiectasis. Sinusitis loads the nasopharynx with infected pus and infects the blood with organisms. Septic tonsils in the adult show ulceration just within the mouth of the crypt, and infiltration of the cryptal epithelium with lymphocytes, which are poured out into the saliva. Few organisms are seen in the crypts.

In the enlarged tonsil of the child there is hypertrophy of the adenoid tissue as a reaction to not very obvious sepsis of the crypts.

In the lacunar tonsillitis of middle age, the large crypts are full of various micro-organisms, and even of actinomyces, but the ulceration and adenoid tissue is small, whilst scar tissue is pronounced. We know that cryptal absorption may lead to septicæmia and other diseases, but, so far as pulmonary and aural infection is concerned, the evidence agrees with Flurin who states that rhinopharyngitis is localized in the tonsils.

For some years I have treated septic tonsils which are unsuitable for enucleation by cupping with a two-way cup exhausted by a pump, and the introduction into the crypts, by negative pressure, of an antiseptic—either hydrogen peroxide or 1 : 10 camphorated phenol. During earlier treatment blood escapes from the ulcers, but these gradually heal, and finally no blood exudes during the treatment. The

patients feel much better afterwards, therefore, presumably, absorption takes place in septic tonsils.

The efficient action of the nose is an important factor in controlling or diminishing attacks of rhinopharyngitis. The association of septic tonsils with nasal obstruction in the adult is well known, and the reduction of rhinopharyngitis on the correction of the nose and enucleation of septic tonsils is a matter of everyday experience.

Normal nasal inspiration yields air saturated with moisture, warmed, and free from ordinary dust and bacteria. Expired air is also free from micro-organisms, but talking, sneezing, and coughing distribute infected droplet spray up to 7 ft. The commonest method of catching a cold is to go from a heated crowded room into cold air. Such a room is full of droplet-spray and dust; the mucous membrane of the nose becomes dry and turgescent, and more mouth-breathing occurs; exposed to cold air the mucous membrane blanches.

Recently two types of inflammation have been described:—

(*a*) The leucocytic, characterized by polymorphonuclear and mucoid outpourings; this is the common catarrhal form and is followed by hypertrophy of connective tissue; it is said to be due to bacterial infection.

(*b*) The serous type, said to be of virus origin and, as such, to occur in influenza; it is characterized by destruction of epithelium and atrophy of connective tissues.

These two types approximate to the vasomotor hypertrophy seen in obstructed noses and to the dry and atrophic rhinitis usual in patent noses.

The milk we consume is pasteurized by the Dairy Companies; the water we drink is filtered and chloramined by the Water Boards. The external air of cities has improved, but crowded cars and dusty houses compel a real communism of micro-organisms.

(1) Infection by inhalation has latterly come to the front.

Gond is of opinion that tubercle bacilli enter by this method: (*a*) Dust may be a factor either as a vehicle of the conveyance of microörganisms or as an irritant combining with bacteria causing infection. Jones has shown that sericite, a silicate of aluminium and potassium, an impalpable powder that floats indefinitely in the air and is not brought down by water spraying, is the cause of miners' phthisis. The particles, 3 microns in size—about the length of bacilli—reach the alveoli and cause tissue change and the formation of fibrous nodules in the lymph-glands. Kettle finds that kaolin is equally dangerous and shows that its particles act as irritants and may be combined with the action of an organism, usually the tubercle bacillus. The concomitant effect of dust may be a factor in cases where massive infection was supposed to be potent. Thus a case of unsuspected cerebrospinal meningitis led to the examination of the orderlies of an isolated block; 13 out of the 15 orderlies were found to be carriers. On the other hand, the unmasked orderlies in a cerebrospinal ward where the windows were open were free of the meningococcus. (*b*) Interference with the efficiency of the cilia is also regarded as a factor, and Proetz and Negus have shown how dryness and acids put the cilia out of action. Noses with dry catarrhs do not, however, show greatly increased infection, except in the case of erysipelas.

(2) Direct extension occurs both in the pulmonary and Eustachian tracts. In a mild degree it follows many attacks of catarrh.

(3) Infection by way of blood and lymph. I do not propose to deal with this section except to note that Blake and Cecil have suggested that primary bronchial infection extends by way of the lymphatics to the alveoli.

(4) I do not propose to deal with sensitization or other biochemical factors.

In the pulmonary tract ciliated epithelium extends from below the vocal cord to, but not including, the cubical epithelium at the alveolar entrance. Briscoe relates that this cubical epithelium has no resistance, while the alveolar epithelium is

sluggishly resistant. Mucus and débris are normally carried to the level of the cords by the cilia, where the débris swallowed is small in amount and screeded if considerable. With inspiration the glottis relaxes and the bronchioles dilate; during expiration the glottis and bronchioles contract. At the beginning of inspiration the alveolar air leaves the alveolus and returns with the main inspiratory wave. In expiration the air first of all enters the alveoli and then leaves the alveoli during the main expiratory effort. In this way the pressure of respired air is controlled and its constituents mixed.

When inflammation affects the bronchioles, the resulting constriction, in addition to the normal contraction of expiration, reduces the air-way—with three possibilities :—

(1) A slight narrowing produces the asthmatoid wheeze.

(2) If the obstruction is increased the check valve is produced in which expiration is impeded. The obstruction to expiration results in dilatation of the alveoli, already softened by previous inflammation, constituting emphysema.

(3) The third of Chevalier Jackson's types is the stop-valve, in which there is complete obstruction in the bronchioles, causing collapse of the lung (atelectasis) and drowning by exudation. The pneumococcus causes such atelectasis and exudation (Henderson).

Jenner, a great opponent of specialism, attributed emphysema to cough; Chevalier Jackson, by bronchoscopic observation, has actually seen the process of obstruction.

As evidence of the frequent infection of the pulmonary tract, it will be noticed how in the later stages of an ordinary catarrh a patient coughs—an indication of the extension to the larynx and the trachea or even lower. Examination of the larynx and bronchi will show catarrhal changes. Radiograph has revealed infection in many unsuspected cases.

A doctor, aged 53, with rheumatism, septic tonsils, and deflected septum, underwent tonsillectomy and resection of the septum. Ten days later his temperature rose and a suppurating antrum full of thick pus was opened, with every precaution to avoid inhalation. For two months the fever ran up to 102° F. Dr. Aston Key could only find a slightly high-pitched note and a few râles. A pellet of sputum came up once a day. A skiagram (Dr. Beverley Bird) shows extensive bronchopneumonia (see fig. p. 4).

Again what little evidence there is of the fatal bronchopneumonia which closes the lives of so many cancer patients!

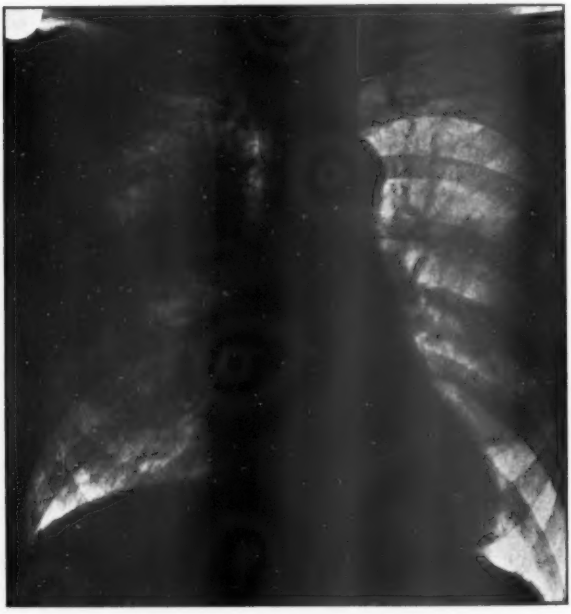
Gaskell has enunciated the view that the extensive change of lobar pneumonia and the patchy infection of bronchopneumonia depend on the virulence and dosage of organisms. The modern tendency is to lay more stress on the virulence of the organism than on massive infection.

A bronchopneumonia may be followed by the gradual development of (*a*) bronchiectasis—a dilatation of the bronchial tubes with ulceration at the entrance to the infected area; this is either due to, or accompanied by, a formation of inflammatory connective-tissue outside the affected airways, or (*b*) a residual effusion into the bronchioles and alveoli of the affected area; this may be gradually resolved, or further infection may determine the formation of a lung abscess.

J. M., aged 8, sent to me by Dr. Pearson, at University College Hospital. Bronchopneumonia three months previously, no cough, no fever; physical signs and radiography showed an unresolved pneumonia at the right base. A rubber-ended suction tube was passed into the area through a bronchoscope tube, and 1 oz. of turgid fluid was withdrawn; the fluid did not contain any living micro-organisms. The child improved but bronchiectasis was suspected. Such an effusion bears some resemblance to the chronic mucoid effusion of the middle ear.

The results of pleural effusions are not dealt with.

The Eustachian tube throughout its 1½ in., and also the floor of the tympanum, are covered with ciliated epithelium. The tube, middle ear, antrum, and pneumatic cells are derived from the first cleft. The attic is said to be cut off from the atrium by an inflammatory swelling of the folds of Trolsch, and the antrum by a swollen narrow aditus. As in the lungs, the peripheral section is the more vulnerable. Much damage may be done to the middle ear and there may be fatal extensions. Luckily the membrana tympani is a safety-valve for the commoner middle-ear infections. Some think that the antrum is affected in most cases of acute middle-ear disease and it is extraordinary how frequent is the tenderness in such cases over the antrum. Pressure on the tip of the mastoid is the more definite sign of involvement of the superficial mastoid cells. Tension and want of drainage probably play more



Bronchopneumonia of right lung—few physical signs.

important parts than damming-off. An infected antrum with a dense mastoid exhibits more pain but less disease than one having the cancellous form. The posterior wall and superior quarter of the anterior wall of the Eustachian tube are covered by the pothook-shaped cartilage, while the anterior and interior walls, to which are attached part of the tensor and levator, are fibrous in character. The anterior and posterior walls of this section are in contact, and the narrowest part is near the outer end of the cartilaginous tube. On swallowing, the inferior and anterior walls are pulled forward and the tube opens. Variations in the entrance of air as indicated by Valsalva or by catheterization is heard as a gradual rush or sudden distension. Such variations may be heard in the two sides of the one individual. They are probably caused by swelling of the mucous membrane or collection of mucus. I have a patient who can normally Valsalva one side only, but subacute catarrh transposes the patency of the two sides. Toynbee's experiment, e.g.

swallowing with mouth and nose closed, followed by an ordinary swallow, is a more efficient way of opening the tubes than Valsalva. I have seen a case in which the Eustachian tube was so wide open that the membrana tympani moved in an outward respiration. Yet there was no obvious middle-ear trouble.

The most definite factors in tubal infection are: (1) In the young, adenoid infection, particularly of the fossa of Rosenmüller where an adenoid mass is adherent to the posterior lip of the Eustachian cartilage.

A child with chronic suppurative otitis media had undergone removal of adenoids and tonsils but the fossa of Rosenmüller was left untouched. The fossa was subsequently cleared and the ear healed in a month's time.

(2) In the adult, acute and chronic pharyngitis are the forerunners of tubal infection. In a case of phlegmonous pharyngitis in which it was necessary to palpate the nasopharynx, the forefinger could only just be introduced into that cavity. The Eustachian tubes were slightly fuller than normal and their margins were ill-defined. It would appear that direct extension, not air-borne infection of the infinitesimal air exchange, is the prevailing method of infection. The tube is further guarded from forcible inflation by the fact that it is impossible to breath while swallowing.

In the ear, by watching the drum-head we have a method of observing the condition of the middle ear, and such observations suggest that the state of the middle ear approximates to that of the nasopharynx. If the drum-head is examined about five days after an attack of nasopharyngeal catarrh it will be frequently noticed that the drum becomes swollen and red vessels appear along the malleus; all that the patient feels is a sensation of fullness or slight bruising in the ear.

In acute catarrh the Eustachian tube has control similar to that exercised by the bronchioles. Contraction of the tube dams off infections primarily, but when middle-ear infection has occurred opening the Eustachian tube is important to secure drainage of the middle ear. I have cut short such attacks of acute otitis media by injecting, per catheter, a few drops of glycerine acid carbolic, 10-1.

Infections of the Eustachian tube may be so severe that the Eustachian tube, middle ear, and external auditory meatus may be attacked at once in a way comparable to extensive pulmonary disease.

In the new-born infant the Eustachian tube is half the length of the adult's and is straight, not concave downwards. Further, the pharyngeal opening is at palate gastro-enteritis in infants, and probably produced directly by vomit passing into level, that is to say, lower. Maizels has reported cases of mastoiditis complicating the nasopharynx. Findlay states that suppurative otitis media is the commonest complication of bronchopneumonia in the child. It is probable that either both Eustachian and pulmonary tracts are infected from the nasopharynx, or sputum is coughed up into the nasopharynx; accordingly the ears of bronchopneumonic children should be examined, but no question of primary and secondary infection is involved.

The treatment, apart from correcting nasal obstruction sinusitis and septic tonsils, falls into headings:—

(1) The hygiene of the upper respiratory tract.

Ung. hyd. nit. dil.	℥ ss
Menthol	gr. x
Ol. olivæ	ad ℥ j

is painted one inch inside the nostrils every night. The oil is carried by the cilia into the pharynx and mixes with the mucus; menthol shrinks-up and anæsthetizes the mucous membrane, while the mercury preparation increases the anti-bacterial properties of the mucus. This preparation not only protects the individual but renders him less infective to others.

In 1915 it was used in the meningococcal carriers when we were unable to obtain a positive cultivation for one week after treatment of a carrier with the oil. A saline lotion may also be given in the morning.

(2) Pharyngitis may be treated with collosol argentum, 1 : 400, sprayed. It is well to include the post-nasal space, larynx, and trachea in this treatment. If there is a trace of asthmatoid wheeze or a sense of obstructed bronchioles, sprays of adrenaline and ephedrine may be used in addition to the treatment prescribed by the physician: bronchovydrin is also helpful.

Vaccines as a prophylactic are useful in many cases. There is sometimes an element of gout in pharyngitis: this should be specifically treated.

(3) Reduction of chronic pharyngitis and emphysema. A slow deep-breathing exercise is employed; it consists of one inspiratory phase and two expiratory phases. The inspiratory phase is deep; in the first expiratory phase the clefts between the thumbs and first finger forcibly compress the sides of the chest, in the second phase the hands slide down, and with thumbs pressed on the chest the outspread fingers compress the abdomen. In the expiratory phases the elbows are turned forward. By this method the movements of the chest and diaphragm are restored and the pharyngeal catarrh reduced.

The patient shown was treated in this way and improvement to pharynx, lungs and ears resulted. Incidentally he can now play two rounds of golf a day, and smoking does not make him cough.

ILLUSTRATIVE CASE

Nasal Obstruction: Descending Catarrh of Lung and Ear

J. K., aged 72. Underwent an operation for relief of nasal obstruction sixteen years ago.

Three years ago had extensive emphysema; ½ in. difference in chest circumference between inspiration and expiration. Congested nasopharynx.

Attacks of otitic catarrh indicated by injection of the drums and a sensation of fulness in the external auditory meatus. Heart-beat irregular.

Under local treatment and deep-breathing exercises the emphysema diminished; there is 3 in. movement of the chest, the pharynx is not congested and the otitis media has disappeared, leaving slightly atrophic drum-heads.

Chronic degenerative labyrinthitis has gradually developed.

Present condition:—

Hearing: R. 18 ft.	...	Conversational voice	...	...	18 ft. L.
$\frac{15}{30}$	...	c. on mastoid ...	...	...	$\frac{15}{30}$
$\frac{53}{70}$	...	c. closing external auditory meatus		...	$\frac{53}{70}$
$\frac{23}{40}$	...	c. value of middle ear	...	...	$\frac{23}{40}$

On the Function of the Tympanic Muscles

By C. S. HALLPIKE, F.R.C.S.

(*From the Ferens Institute of Otology, Middlesex Hospital*)

IN 1864 there was published an account by Adam Politzer [1] of what must be considered the first significant investigations of the function of the tympanic muscles. After a lapse of seventy years it is difficult to read Politzer's account without admiring the grasp of physiological methods displayed in these experiments by a practical otologist, and Politzer's work can properly be regarded as constituting the foundation of our present knowledge of the subject.

Politzer investigated the innervation of the tympanic muscles, and he noted the disturbance of the labyrinthine fluids set up by contractions of the tensor tympani produced by electrical stimulation of the fifth nerve in the dog.

In addition, he observed the effect of such contractions upon the transmission of sound-waves by the simple method of auscultation of the tympanum via a tube sealed into a hole bored in the bulla of the animal. In this way he was able to report that contraction of the muscle appeared to exercise a damping effect upon sound-waves passing across the tympanum.

At this time the fact that the tympanic muscles reacted reflexly in response to auditory stimuli was not known, but was discovered soon after by Hensen [2]; Köhler [3], extended these observations to man, and later, Kato [4] and Kobrak [5] have investigated the subject very fully in the cat and rabbit.

Although at present the fact of the reflex response of the muscles to auditory stimulation is fully substantiated, the further and more important question of the effect of such contractions upon what goes on in the internal ear has not been answered so satisfactorily. Although most important investigations, such as those of Politzer and Kato, attribute to these contractions a protective function, the opposite view that the muscles are concerned in increasing the sensitivity of the internal ear, as in listening, still finds support. That opinions so diverse should be in circulation finds its explanation in the inherent difficulties of obtaining any objective assessment of the working of the internal ear. The present paper deals with some experiments carried out by Mr. Rawdon-Smith and the writer [6], in which an attempt has been made to overcome this deficiency by investigating the effect of reflex contractions of the tympanic muscles upon certain electrical changes set up in the internal ear in response to physiologically applied sound-waves, changes which have come to be known after their discoverers as the Wever and Bray phenomenon. Without dealing extensively with all that has been said concerning the origin and biological significance of the Wever and Bray phenomenon, it will nevertheless be necessary to describe briefly some of the more important aspects of what is now known.

Micro-potential changes are generated within the intact mammalian cochlea in response to sound-waves. The potential changes reproduce accurately the frequency of the sound and the phenomenon is in this sense a microphonic one. With appropriate amplification, speech and music may be reproduced upon a loud speaker.

The central question demanding solution has concerned the origin of the potential changes. Although within the last two years most of the evidence has rather contra-indicated the important possibility that the changes are generated by the neural elements of the cochlea, some recent experiments seem to show that this possibility is one which must still be seriously considered.

Witmaack [7] found that section of the eighth nerve in the cat led to degeneration of the neural elements of the cochlea. We have found that this occurs in some cases, but that the issue is much confused by the effects of section of the internal auditory artery which usually accompanies division of the nerve. Such section of the artery leads to massive necrosis of the entire cochlear contents, with the formation, in some cases, of masses of heterotopic new bone. When, however, the nerve is cut without division of the artery, there occurs an isolated degeneration of the neural elements of the cochlea, with preservation of all other cochlear structures. In such a cochlea, the Wever and Bray phenomenon has been found to be absent [8].

It would appear likely, therefore, that normally functioning nerve elements are required for the production of the Wever and Bray phenomenon. But whatever the ultimate solution of the problem, it is sufficient at present to regard the phenomenon as something of vital significance, and moreover as something which goes on in the internal ear which can be assessed in an objective way, and should thus provide us with a key to the problem of the intracochlear effects of reflex contractions of the tympanic muscles.

The technical procedure employed in these experiments is shown in fig. 1. Sound from a source controllable for frequency and intensity is led into the external ear of a decerebrate cat via a brass tube securely tied into the meatus. The tympanic cavity is exposed by dissection, and viewed through a low-power binocular dissecting microscope. An active electrode is placed upon the round window margin, whence it is led to the input stage of a high gain amplifier of conventional design. The output of the amplifier is connected to a cathode-ray oscillograph.

The sound passing to the cat's ear is led by way of a brass cross-piece, one limb of which passes to a microphone.

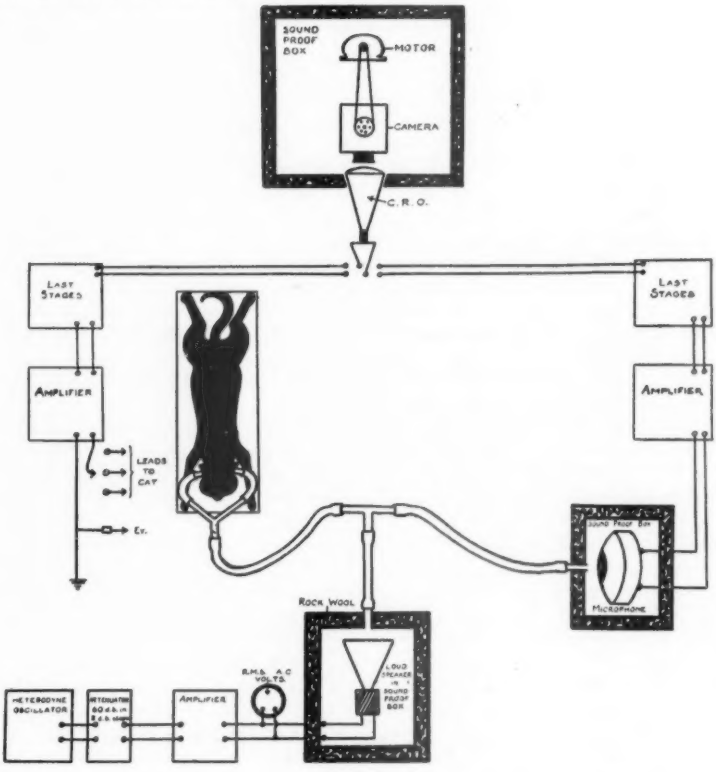


FIG. 1.

The output of the microphone passes to the input of another amplifier, the output of which may also be connected to the cathode-ray oscillograph. Thus a record may be obtained, not only of the sound passing into the animal's ear, but also of the electrical response to such sound.

The contractions of the tympanic muscles are observed through the dissecting microscope. Fig. 2 shows the view so obtained of the operative field. The tympanic muscles are observed to contract briskly in response to sounds over the range of 500~—2,000~, of an intensity some 70 or more decibels above the human threshold. Less brisk responses can, however, be observed over a much wider range of frequencies.

The response, as observed through the microscope, consists of an initial twitch, a sustained tetanic contraction and a terminal twitch when the sound ceases. Although crossing of the reflex contractions is described by Kobrak, and more lately by de Nó [9] in the case of the rabbit, these, we find, do not generally occur in the cat.

Coming finally to the results of these experiments. Fig. 3 shows records of the Wever and Bray response at the onset of trains of sound-waves, the tympanic muscles being active.

In Record 1, full amplitude of the cochlear response is rapidly attained, the presence of well-marked overtones being a conspicuous feature. Within a period of some 10 σ after the beginning of the stimulus, there ensues a rapid decrease in

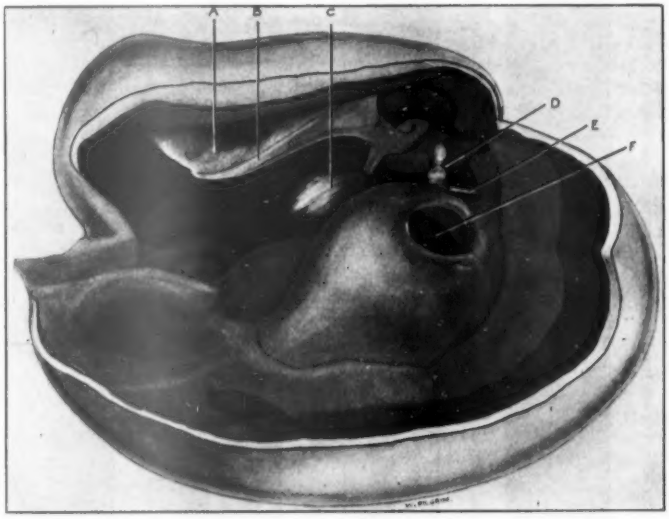


FIG. 2.

A. Tympanic membrane.
B. Long process of malleus.
C. Tensor tympani.
D. Incudo-stapedial joint.
E. Stapedius.
F. Round window.

amplitude of successive waves, with a well-marked tendency to elimination of the overtones. This decrease reaches its maximum at a point some 30 σ after its initiation, and thereafter the amplitude shows a gradual increase, but its initial value is never regained.

In Record 2, the intensity of the sound stimulus was greater, and the decrease in amplitude of the response after the initial waves is relatively accentuated.

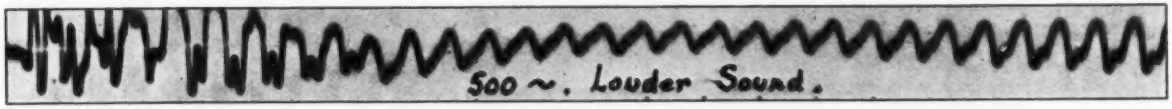
In Record 3, a relatively low intensity of a frequency of 1,000~ was employed as a stimulus. The decrease of amplitude of the response after the first few waves is seen to be less in degree and of more gradual onset.

That the changes in amplitude and wave-form displayed in these records must be attributed to the contractions of the tympanic muscles observed through the microscope to occur during the taking of these records is shown by Record 4. In this the reflex contractions of the muscles were eliminated by chloroform inhalations.

FIG. 3.

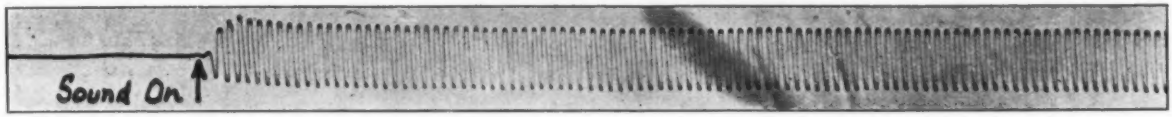
Oscillograph records showing the action of reflex contractions of the tympanic muscles upon the Wever and Bray response.

1. Frequency 500 ~. Showing damping action of tympanic muscles with partial elimination of overtones.



2. Frequency 500 ~. Higher intensity. Showing accentuation of damping action of tympanic muscles.

3. Frequency 1,000 ~. Relatively low intensity. Showing slower onset and less marked degree of damping.



4. Frequency 1,000 ~. After chloroform. Reflex contractions of tympanic muscles absent. Showing absence of damping action.

Following this, the changes in amplitude and wave-form displayed in Records 1, 2 and 3, were found to be eliminated, the response now sustaining its full amplitude in an entirely unbroken manner.

The following conclusions can be drawn from these records :—

Firstly that since the reflex contractions of the tympanic muscles occur in response to sounds of fairly high intensity, the theory of their action as increasing the sensitivity of the ear, as in listening, seems *a priori* unlikely.

Secondly, that the contractions do in fact exert a protective damping effect upon sound vibrations reaching the internal ear is proved by the conspicuous decrease in amplitude of the electrical response of the cochlea brought about by these contractions.

Thirdly, it has long been known that the sensation resulting from a compound tone generated by a number of pure tone generators may undergo no distinguishable change when one or more of its components are withdrawn, and it has been suggested that the missing overtones are in some way re-created by the vibrating elements of the ear. That the vibrating system of the ear is capable of manufacturing such overtones is shown by the fact that, whereas microphone records of the stimulating tones employed in Records 1, 2, 3 showed them to be of approximately sinusoidal wave-form, the records of the cochlear response to these tones showed a marked overtone content.

In conclusion it will be noted that nothing has been said of the individual action of the two tympanic muscles, though much attention is devoted in the literature to this problem. For the present, however, it has been thought of greater physiological significance to study the action of the two muscles acting physiologically, that is to say, together.

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Discussion.—The President said that Mr. Hallpike's paper marked a new period in otology. The Wever and Bray phenomenon had opened up a new criterion by which the functions of the various parts of the ear could be assessed, and Mr. Hallpike had shown that the tensor tympani and the stapedius controlled overtones and quick damping of sounds. It had been said that speech destitute of overtones would be unintelligible.

It was assumed that the tensor tympani increased, and the stapedius diminished, the labyrinthine pressure, and he, the speaker, regarded the tensor tympani, the chain of bones and the stapedius as a joint system braced by the muscles.

Mr. F. J. Cleminson said he would like to know whether Mr. Hallpike had found evidence to show that the two muscles of the middle ear reacted as antagonistic groups of limb muscles did—i.e. that as one came into action the other underwent reflex inhibition.

Applying what Mr. Hallpike had said to the mechanism by which speech was heard, it was clear that the fleeting action of these muscles in damping-down the harmonics was the very one which Nature might be expected to provide. The sounds of everyday life were seldom continuously uniform, either in intensity or pitch; what was heard was a series of rapidly changing sounds, as in speech. The middle-ear muscles seem to have been designed to perform the function of damping-out the excessive vibration and harmonics for the successive instants necessary for the hearer fully to appreciate each particular stage of the rapidly-changing sound.

Sir JAMES DUNDAS-GRANT said he wondered whether many had had actual observation of cases of apparent inaction of the stapedius. He remembered the mother of a family who had facial paralysis. The paralysis passed off, but at the time the noises made by her children were a source of acute pain to her, showing, he thought, that in her case the damping effect of the stapedius had been cut off.

In none of the experiments hitherto had there been a demonstration of the behaviour of the round window when there was ankylosis of the stapes. He had had a case in which the stapes was ankylosed—as far as diagnosis went—and in which he produced a lasting opening or perforation in the tympanic membrane, showing the round window exposed. In such a case as that one could judge, to some extent, of the action of the round window, through which a good deal of hearing could be carried out, perhaps all the better because the round window was exposed and the stapes was ankylosed.

Mr. F. WATKYN-THOMAS said that one very important practical point was raised in Mr. Hallpike's paper. All otologists had found, when performing the conservative mastoid operation, cases in which the incus was simply lying loose in granulation tissue. The incus was removed, and the patient's hearing was, if anything, better; certainly it was very rarely worse. What interested him particularly was the after-fate of the ears of those patients when they had lost the incus, and hence were largely without the important protective mechanism, when they were subjected to continuous noise. He would like to hear what Mr. Hallpike had to say on this point: he did not know whether any work had been done on it. Such patients would still have their stapedius, but their tensor tympani would be no longer of help to them.

Dr. DOUGLAS GUTHRIE asked whether Mr. Hallpike had investigated separately the function of each of the two intra-tympanic muscles. It was naturally assumed that they acted in unison and fulfilled similar functions, but this could only be confirmed by experiment. Had Mr. Hallpike divided one, leaving the other intact and if so, what effect had he noted?

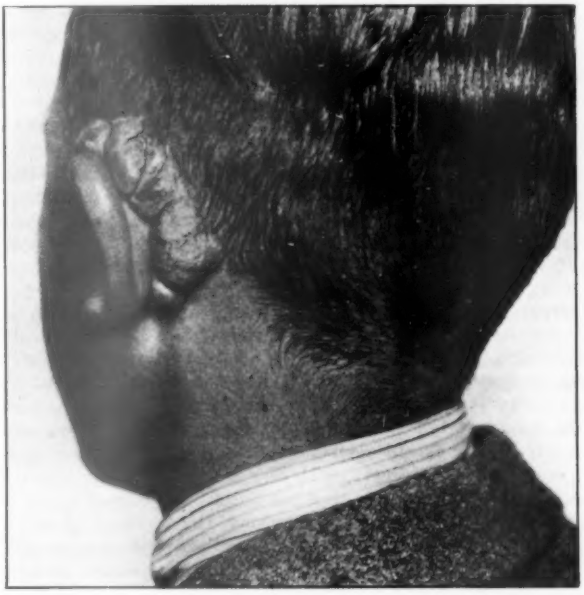
Mr. THACKER NEVILLE remarked that Mr. Hallpike stated that he abolished contraction of the tensor tympani with chloroform or with the diathermy knife, and he, the speaker, would like to know how he stimulated it. Did Mr. Hallpike employ sound alone, and if so did low notes cause relaxation and high notes contraction?

Mr. HALLPIKE (in reply to Dr. Douglas Guthrie) said that the experiments he had been describing represented the effects of contraction of both the muscles acting together. No attempt had been made to differentiate between them; that would be a very difficult thing to do satisfactorily. If one cut the tendon of one muscle, the whole working of the middle-ear mechanism was changed, and at the moment it was not found to be worth while to cut the tendons. The only way was to paralyse muscles individually, so that their resting tension would not be changed very much.

In answer to Mr. Cleminson: Both tympanic muscles, as observed under the microscope, appeared to contract together. If the tensor tympani tendon was cut and the muscle allowed to retract, its stump was observed to contract as vigorously as before on stimulation of the ear with sound. He believed that it had been suggested that the contractions of the tensor tympani described were tendon reflexes, as in the case of the knee-jerk. This, however, was not correct, since following section of the tendon the stump of the muscle continued to react vigorously. In reply to Mr. Thacker Neville: The form of stimulation used was sound falling on the ear. In reply to Sir James Dundas-Grant: Immobilization of the stapes was not easy to effect. Mercury beads could be dropped into the oval window recess, but it seemed likely that the mercury would be free to move with the stapes. Drops of plaster of Paris had been tried, but this, on drying, became loose from the walls of the cavity and was not satisfactory in practice. In reply to Mr. Watkyn-Thomas: Regarding the effect of continuous noise upon the internal ear following the removal of the incus, Von Eicken had shown that after this operation on one side, in the guinea-pig, long continued exposure to sound failed to produce degenerative changes in the internal ear on the side of the operation, but did produce these changes in the opposite normal ear. It seemed likely, therefore, that removal of the incus would in itself bring about a high degree of protection of the internal ear from the effects of prolonged loud sounds. Compared with this protective action of removal of the incus, the question of the protective action of tympanic muscles would probably not arise.

Large Keloids on Mastoid Scars.—DAN MCKENZIE, M.D.

Boy, aged 15. Double cortical mastoid operation in 1932. Under treatment by diathermy. It is interesting to note that he shows also a keloid scar on the leg.



Mastoid keloid after cortical mastoid operation, bilateral.

Discussion.—Mr. F. C. CAPPS said that the case was still under treatment by diathermy coagulation, and the recent report of the pathologist was that the section resembled fibroma rather than keloid in structure.

Mr. HERBERT TILLEY said that cases of keloid scars after mastoid and other operations had for many years been treated successfully at the Radium Institute by surface radiation.

Mr. RITCHIE RODGER agreed with Mr. Tilley that radium was the best method of treatment for keloid formations. He had seen only one case out of some 1,800 mastoid operations, so that the condition must be comparatively rare. In that case, as in Dr. McKenzie's, the patient, a youth of 23, had another keloid scar; this was on his back. A dermatologist who saw the case suggested that there might be a tuberculous diathesis, and the family doctor then informed him that the boy had slept in the garden for some years, his father having had tuberculosis of the lung. He (the speaker) had tried a radium plaque at first, but without success. He then plunged eleven 0·5 mgm. needles vertically in the scar, about 1 cm. apart, retaining them seven days. Gradual diminution occurred and then at the end of eight months the swelling had quickly receded and disappeared. When the patient was seen lately, after two and a half years, there was no trace of keloid.

Labyrinthitis. Concealed Cholesteatoma. Carious Patch on Petrous Bone revealed by X-rays.—DAN MCKENZIE, M.D.

Correct diagnosis in this case was delayed for eight weeks by reason of the absence of any discharge from the external auditory meatus during the time of observation.

A woman, aged 35, had had a radical mastoid operation on the *left* ear performed by me in 1932 for cholesteatoma with the labyrinth fistula symptom. Rapid and complete cicatrization had followed.

In March of the present year she was suddenly seized with a violent labyrinth storm in the course of which I saw her. The onset, along with the vertigo, of severe tinnitus and nerve deafness in the *right* ear showed that ear to be the source of her symptoms.

There was no discharge from it, however, nor had there been any for two years. The tympanic membrane showed the typical cholesteatomatous sinus in its postero-superior quadrant and adjoining meatal wall. But all was dry and cicatrized and there was no pain.

In three or four days the acute symptoms subsided, but a feeling of imbalance persisted ; and, as time went on, several other crises occurred though much less severe than the first, and the deafness remained.

Every obvious cause of labyrinth disease having been as far as possible excluded, and the symptoms continuing, it was decided at the end of May to explore the ear surgically.

As a preliminary, X-ray examination of the labyrinth was made by Dr. Graham Hodgson, who reported : "There is a hazy appearance of the capsular bone of the right labyrinth which is unlike that seen in otosclerosis, and is chiefly affecting the capsule of the superior canal." . . . "It may be caused by an acute infection, but there is no X-ray evidence of infection of the right mastoid process."

Fortified by this report, I performed a radical mastoid operation on the right ear. A moderately large mastoid cavity, empty and with dark and jagged bony walls was disclosed, communicating freely with the antrum. No granulations were to be seen anywhere, the bone being quite dry and bare. But lateral to the superior canal, that is to say, at the precise spot indicated by Dr. Graham Hodgson, a patch of disintegrated bone, about 1 × 3 mm. in area, was found and removed with a fine curette, the superior canal not being opened as far as could be seen. The bony granules were of the sand-grain kind found typically in cholesteatoma, and on the floor of the aditus one small patch of cholesteatomatous membrane was identified. The tympanic cavity was equally dry and void of granulations, scar-tissue only being present, in which a fragment of the malleus was embedded. The labyrinth was not opened.

The operation was followed by immediate disappearance of all giddiness, and as time has gone on even the hearing has shown some improvement. Tinnitus remains unchanged.

Attention is drawn (1) to the "Ménière" syndrome arising from latent cholesteatoma ; and (2) to the discovery by X-rays of a minute patch of caries on the outer labyrinth wall. The bearing of this latter fact upon the value of X-ray examination of the labyrinth not only in cases of otosclerosis but also in cases with Ménière symptoms needs no emphasizing.

Acute Exacerbation of Chronic Suppurative Otitis Media. Extradural Abscess. Complete Hemianopia.—F. C. W. CAPPS, F.R.C.S.

D. W., aged 18, cabinet-maker, admitted to Hackney Hospital, September 16, 1934.

History.—Chronic right otorrhœa "all his life" without pain in the ear. Two weeks ago began to be troubled with pain in the right ear, from which, a few days afterwards, there was a profuse yellow discharge which continued for a week and then ceased. Three days later pain commenced in the right temporal region. Patient had occasional attacks of giddiness and mistiness over the eyes. Feels sleepy but has not slept. No vomiting.

On examination.—General condition fair. Temperature 101·8° F. Circulatory system : Bradycardia ; pulse 50. Respiratory and digestive systems normal.

Central nervous system : Drowsy. Very definite tenderness over right temple. Little mastoid tenderness. Complete hemianopia to the left. No motor or sensory loss. No stereognosis or loss of sense of movement. Tonus normal. No cranial nerve paralysis. No nystagmus ; no head rigidity.

Lumbar puncture : Cerebrospinal fluid clear ; not under pressure. Pathological report on cerebrospinal fluid : No excess of cells. No excess of globulin. Protein 0·05%.

Right ear : Chronic otitis media.

16.9.34 : Complained of pain in right temporal region. No neck rigidity. Temperature 102·8° F. Pulse 80-64.

Operation.—Radical mastoid. Thick pus in small mastoid antrum. Lateral sinus normal but far forward. Antrum very deep and bone much sclerosed. Long aditus. Cholesteatoma. Dura mater widely exposed. Pulsated well—no obvious tension. Small extradural abscess in middle fossa above the attic. About ℥x of stinking pus. Antrum and tympanum packed with " bipped " gauze ; pack also placed through posterior wall of auditory meatus. Specimen of pus taken for laboratory examination and culture. Report : Swab dried—no direct film made. Cultures grew *Bacillus proteus*, probably owing to contamination. Both cultures showed some Gram-positive cocci but it was impossible to isolate these, owing to the presence of *B. proteus*.

17.9.34 : Complains of some stiffness of neck. Can flex neck a little. Pupils equal, react to light. Reflexes normal. Temperature 99° F. to 100·8° F. Pulse 80-64.

18.9.34 : No diplopia. Pupils normal. Feeling better. Flexion and rotatory movements of head improving. Quite sensible in conversation. Hemianopia appears much less. Temperature 99° F. to 99·6° F. Pulse 64-54.

After this date, the patient made a gradual uninterrupted recovery, with full field of vision.

10.10.34 : Ophthalmoscopic examination (Mr. Arnold Sorsby) : The fundi are normal but require watching. The margins of the discs, especially of the left, are hazy. Probably a physiological variation. No nystagmus.

Mr. A. B. PAVEY-SMITH said that he had had a similar case recently. There was chronic suppurative otitis media on both sides. The patient had been sent to him because of pain in the left ear three days after his doctor had syringed it. When he arrived at hospital he was apparently very deaf ; his inability to answer questions turned out, however, to be due to aphasia. His ear was dry, but there were a few granulations in the attic region. There was no mastoid tenderness. He (the speaker) operated on the patient the same day, and found cholesteatoma and an extradural abscess, which contained about 2 drachms of pus. The dura mater was red over an area of 1 cm. The whole condition cleared up rapidly, and the aphasia recovered in four days. There was no sign of paralysis in any other part of the body. It was apparently an early case of cerebral œdema.

Temporosphenoidal Abscess. Pus in Cerebrospinal Fluid. Drainage of Abscess. Recovery.—MAURICE SORSBY, M.D., F.R.C.S.

L. C., aged 17. Admitted to St. Andrew's Hospital, June 10, 1934, complaining of (1) drowsiness, (2) vomiting, and (3) a high temperature (104° F.).

Previous history.—Otorrhœa for many years ; deafness, which has increased considerably of late.

Present history.—May 10 : Severe pain in right ear, lasting for three days. Diagnosis : " Meatal boil." June 9 : Sudden onset of vomiting. June 10 (on admission) : Temperature 104° F. ; pulse 92 ; respiration 20.

Patient was very drowsy ; could be aroused only with great difficulty, and exhibited great irritability when disturbed.

Central nervous system: Neck rigid and retracted. Patient preferred to lie on the right side. Knee-jerks practically absent; plantar reflexes flexor. Optic discs normal.

Lumbar puncture: Cerebrospinal fluid, opaque and not under pressure. *Pathologist's report on fluid* (Miss K. M. Collis): Pus cells present in such large numbers that they could not be counted; protein 15%. Globulin: present in excess. Chlorides: 720 mgm. per 100 c.c. Organisms: None seen in direct film; culture report negative.

White blood-cell count: Leucos. 16,600; *Differential:* Polys. 77%; lymphos. 22%; large hyals. 1%.

Ears: Both drums destroyed. Right ear: dry, attic perforation; left: profuse discharge. No mastoid tenderness could be elicited.

Operation.—In view of the recent history of pain in the right ear, and absence of otorrhœa in that ear, it was decided to explore the right mastoid. This was found to be a large abscess cavity, containing much pus under considerable tension. The dura was bulging, tense, and of a dark brown colour covered with granulations. The mastoid antrum was filled with cholesteatomatous masses. The brain was explored, and a large quantity of greenish offensive pus was evacuated. Two drainage tubes were inserted.

Pathologist's report on pus from brain abscess: Pneumococci and coliform bacilli seen in film. Culture: *B. proteus.*

Subsequent history.—Patient made an uneventful recovery.

Congenital Abscess of the Ear, with Facial Paralysis.—T. A. Clarke, F.R.C.S.Ed. (by courtesy of Mr. Lionel Colledge).

Patient is a male infant, aged 1 year 6 months. On the left side there are some irregular cartilaginous nodules representing the auricle, but the ear is poorly, if at all, developed.

The left side of the face is paralysed, and there is slight facial asymmetry. There are no other deformities, and no other nervous defects are present.

Nerve-Graft in the Treatment of Facial Paralysis: Ballance and Duel Method.—Sydney Scott, M.S.

S. F., a child aged $2\frac{3}{4}$ years, was first seen at St. Bartholomew's Hospital, April 20, 1933, on account of discharge from the left ear, of eighteen months' duration.

May 12, 1933: Tonsils and adenoids removed by Mr. W. Bell, House Surgeon to the Throat and Ear Department.

December 14, 1933: The child was brought to the hospital again, as the discharge had continued. X-ray examination showed extensive pneumatization of the mastoid, the cells being abnormally opaque.

February 20, 1934: Admitted as in-patient. Next day Schwartze's operation was performed. The mastoid cells were large and extensive, and contained blackish material on swollen mucosa, with pus and mucopus in the antrum and in the zygomatic and apical mastoid cells. Amongst a chain of cells running vertically down from the antrum was found a dehiscence of part of the Fallopian aqueduct, exposing the facial nerve in a bed of vascular mucosa. A discussion took place as to whether the nerve could be identified; it was possible to do so only after it was divided; the lumen of the lower part of the Fallopian aqueduct admitted a small stylet, from above. As it was impossible to bring the ends of the facial nerve into apposition, it was decided to apply a nerve-graft in accordance with the Ballance-Duel method. The Schwartze operation was concluded and the cavity was partly closed, and tube-drained.

Any possible doubt as to the division of the facial nerve was settled by the complete paralysis of the child's face next day (*see* fig. 1).

February 23, 1934: My colleague, Mr. Rupert Corbett, isolated about an inch of a branch of the anterior lateral cutaneous nerve of the child's right thigh, over the upper part of the sartorius muscle. The nerve was divided above a ligature, which was intended to serve as a means of identification a fortnight later.

March 7, 1934: The attempt to identify the divided cutaneous nerve failed. Mr. Corbett therefore isolated another branch of the cutaneous nerve and, at my suggestion, slipped over its distal end a small rubber tube, which was buried in the wound, to ensure subsequent identification.

March 21, 1934: Mr. Corbett reopened the femoral wound and immediately identified the prepared nerve by withdrawing the tube. He removed about three-quarters of an inch of the distal part, placed it in warm normal saline solution and closed the wound.

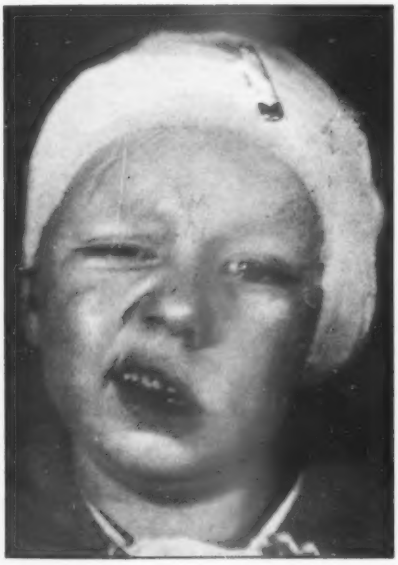


FIG. 1.
February, 1934. Before grafting operation.

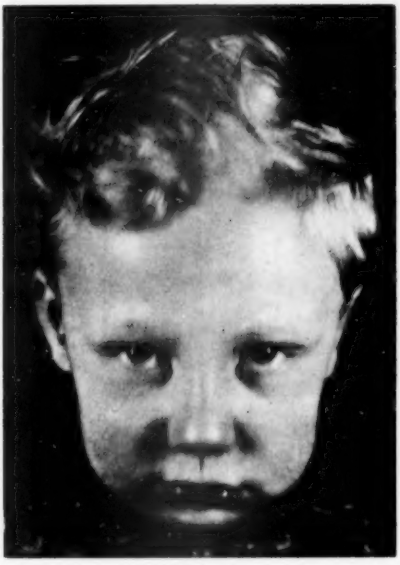


FIG. 2.
17.11.34. Face muscles at rest.

Having reopened the mastoid, and identified the Fallopian aqueduct and the proximate end of the facial nerve, I inserted about a quarter of an inch of the prepared nerve-graft into the gap of the facial nerve, after freshly dividing its proximal end. It was possible to retain the graft in position by placing strands of "bipped" cotton in the external auditory meatus, the posterior wall of the osseus meatus having been removed. No gold foil was applied. The upper two-thirds of the mastoid wound were closed. Except for the removal of outer dressing the wound was undisturbed until the eighth day, when the shreds of cotton-wick were withdrawn.

April 5, 1934: The child was transferred for facial treatment to the Massage Department where massage and electrotherapy were carried out twice a week until the end of October.

May 24, 1934: The child's mother first detected an improvement in the face. In June it was possible to be certain of restoration of tone of the orbicularis muscle.

A note early in October runs: "All face movements much improved; can almost shut the eye voluntarily."

November 1: "Can purse the lips and close the eyelid and frown." (Figs. 2, 3, 4.)

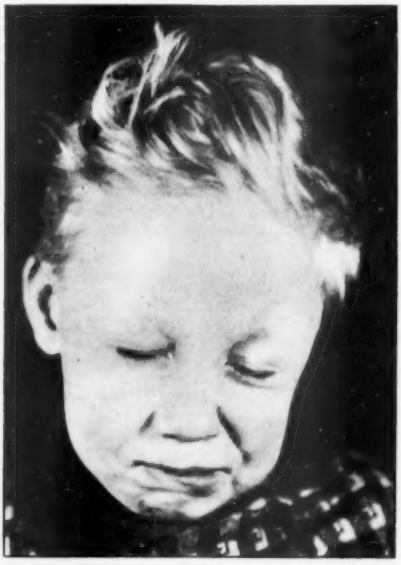


FIG. 3.
17.11.34. Shutting eye tightly.

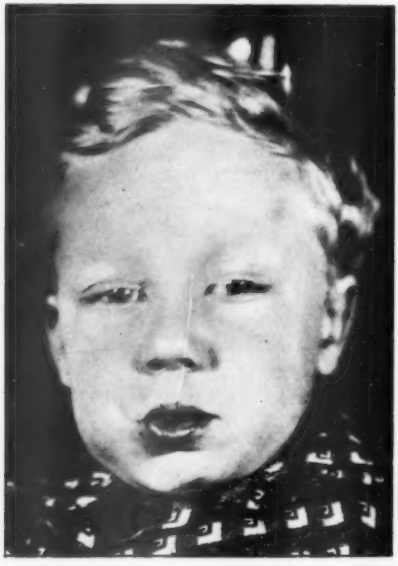


FIG. 4.
23.11.34. Whistling.

Discussion.—The PRESIDENT congratulated Mr. Scott on the result. Dr. Duel had exposed the greater part of the temporal course of the facial nerve by removing the bone as far as the stylo-mastoid foramen. It was a wonder of surgery that a nerve could be restored in a septic field. During the War, nerves and bones had been most easily affected by sepsis. Sir Charles Ballance had said that in these cases it was essential that the operator himself should dress the wound daily.

Mr. SCOTT said that he had shown this patient (1) as an example of the beneficial results of the Ballance-Duel method of nerve-grafting for facial paralysis; (2) because it illustrated certain points in technique, which, he claimed, simplified the operation and identification of the nerve-graft. Dr. Duel[1] had expressed the opinion that to ensheath the divided cutaneous nerve in a rubber tube which was left in situ for a fortnight would interfere with the rapid degeneration of its axis cylinder which he desired, but the successful recovery of the facial nerve functions demonstrated that there could be no such objection as Dr. Duel feared. The success was really due to Sir Charles Ballance's and Dr. Duel's procedures which he (Mr. Scott) had copied in all essentials.

[1] Stockholm, September 1934, Meeting of Collegium Oto-Rhino-Laryngologica.

Section of Orthopædics

President—ALAN H. TODD, M.S.

[*November* 6, 1934]

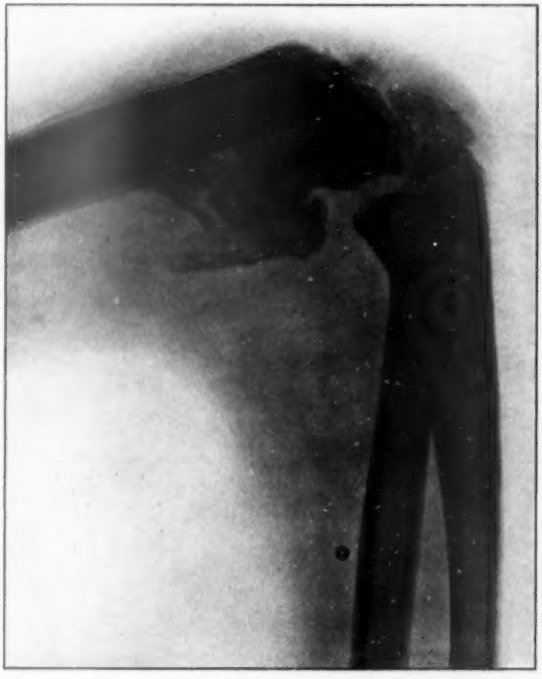
Myositis Ossificans Traumatica.—E. LAMING EVANS, C.B.E., F.R.C.S.

B. D., a boy aged 13.

10.10.32: While playing football, sustained supracondylar fracture of left humerus.

31.10.32: Open operation elsewhere, without reduction of fracture.

30.11.32: Referred to me in Orthopædic Department at Ealing Hospital. Range of movement 5° on either side of right angle. Skiagram (fig. 1) showed large mass



30.11.32.

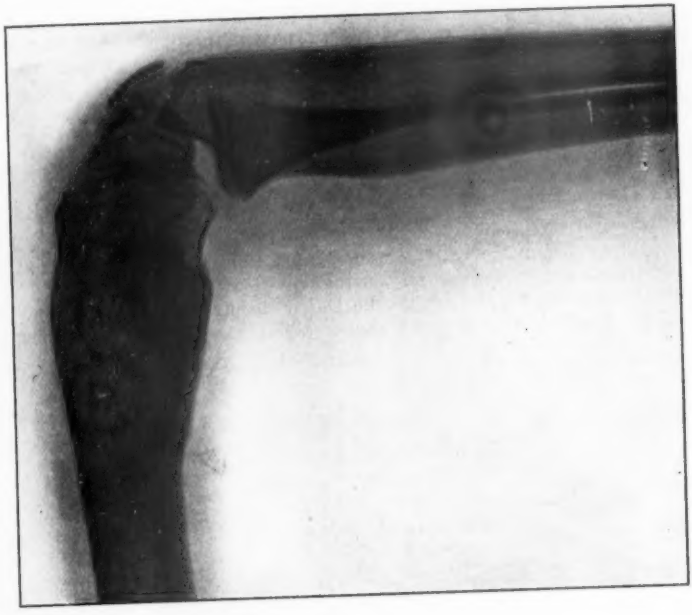
FIG. 1

of new bone and unreduced fracture. Treated by absolute fixation in plaster of Paris until

7.6.33: Operation for removal of new bone.

21.6.33: Skiagram (fig. 2) showed extent of removal of new bone. A few fragments embedded in the muscles were inaccessible and were left.

11.10.33: Flexion and extension movements through arc of 90°.



19.9.34.

FIG. 3.

21.6.33.

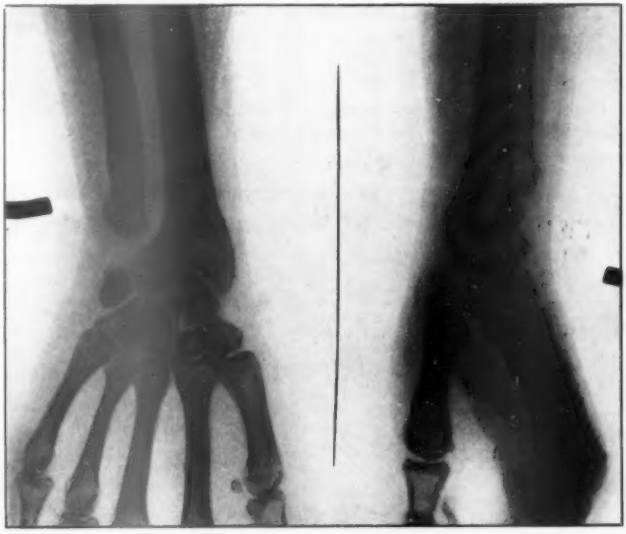
FIG. 2.

28.3.34: Flexion and extension movements through 120°. Throughout, active exercises only were employed; no massage or passive stretchings were permitted.

19.9.34: Skiagram (fig. 3) shows complete absorption of new bone-formation. There is full range of movement at the elbow. At no time was there any limitation of pronation and supination.

Deformity of Wrist Following Injury.—E. HENRIETTA JEBENS, F.R.C.S.

E. S., a girl aged 15, sustained an injury to her left wrist at the age of 6 years. Since then she has suffered from weakness and pain on using the hand. The injury was treated at hospital for two months but, unfortunately, the notes and skiagrams are not obtainable. While at school the disability did not trouble her very much, but now she wishes to take up needlework, and finds she is unable to do so owing to the weakness and pain.



Antero-posterior view showing deformed head and absent styloid process of ulna.

Lateral view showing dorsal dislocation of head of ulna.

On examination.—The left forearm and hand are less well developed than the right. The head of the left ulna is more prominent on the dorsum of the wrist than the right and there is laxity of the inferior radio-ulnar joint. The internal lateral ligament of the left wrist is not palpable. Dorsiflexion and full supination and pronation are limited and painful.

Skiagram.—The left ulna is stunted in growth and the styloid process is absent. There is a subluxation of the ulna backwards at the lower radio-ulnar joint. The lower end of the ulna is thickened and shows some decalcification.

The condition bears a superficial resemblance to a Madelung's deformity. There is weakness of the wrist associated with dorsal subluxation of the head of the ulna and laxity of the lower radio-ulnar joint, but there is no bending forwards of the radius and there are marked changes in the lower end of the ulna, in both the metaphysis and the epiphysis.

The history suggests that the condition results from a trauma ten years ago when the child was between 5 and 6 years of age, and the lower epiphyseal centre of ossification for the ulna was only just about to appear. At the time of the injury, therefore, the greater part of the head and the whole of the styloid process would still have been cartilaginous. The child's mother believes the injury to have been a fracture, but I have been unable to substantiate this, as the notes are not available. I suggest that epiphyseal injury may have produced the deformed head of the ulna and that rupture of the internal lateral ligament, and hence absence of pull, caused the suppression of the styloid process. I am, however, at a loss to account for the condition of the metaphysis. It is, of course, possible that the injury was merely incidental and that the condition is really congenital or due to an obscure bone disease, but I have searched the literature in vain for a similar case.

The Wassermann reaction is negative.

As regards treatment I should be very grateful for any suggestions. She has worn a strap to support the wrist, but finds this useless, as it does not afford sufficient relief for her to carry on her work.

Myositis Ossificans of Elbow.—S. A. S. MALKIN, F.R.C.S.Ed.

29.8.33: Dislocation of right elbow. Reduced. Considerable swelling and contusion around joint—movements very limited and painful.

X-ray examination was negative (Fig. 1).

FIG. 1.
F. P., 30.8.33.
Skiagram immediately after reduction of dislocation of elbow.

Treated in a sling—followed one week later by massage and movements.

4.10.33: Movements had steadily increased—but flexion and extension were still restricted by 45°. Treatment was discontinued.

10.1.34 : Flexion full—extension limited by 30°.

2.5.34 : Patient complained of some pain and thought the elbow was becoming larger. A spur was palpable in front of the joint.

Movements : Flexion full—extension limited by 30°.

A skiagram showed a bony spur in front of the elbow-joint (Fig. 2).

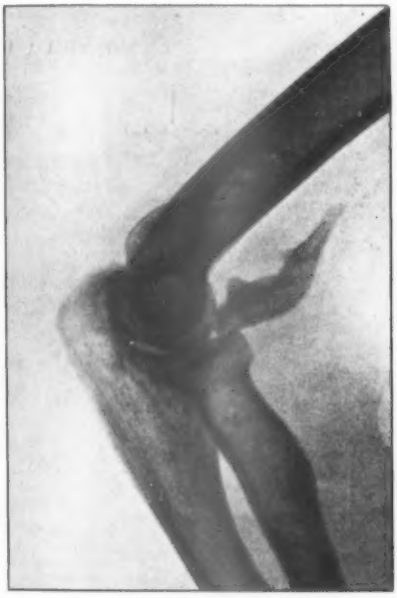


FIG. 2.
F. P., 2.5.34.
Nine months after dislocation of elbow.

FIG. 3.
F. P., 1.8.34.
Twelve months after dislocation of elbow, three months after previous skiagram. During this time the elbow had been immobilized in plaster without any effect.

Plaster of Paris applied. Continued for three months.

21.9.34 : A skiagram showed that the spur was still present (Fig. 3). No alteration in size. 30° of movement in elbow-joint. Operation advised.

Köhler's Disease of Second Metatarsal (Bilateral).—S. A. S. MALKIN, F.R.C.S.Ed.

P. M., a girl aged 14.

First seen 2.12.32, complaining of pain in fore-part of left foot. She said that this had troubled her for the previous three months.

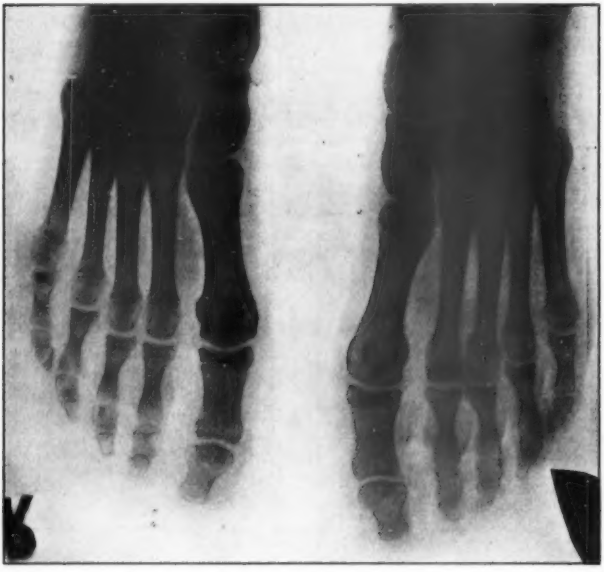
On examination.—Tenderness of head of second metatarsal (left).

X-ray examination.—Left foot : flattening of head of second metatarsal commencing. Right foot normal.

Treated with felt pad and strapping to support anterior arch.

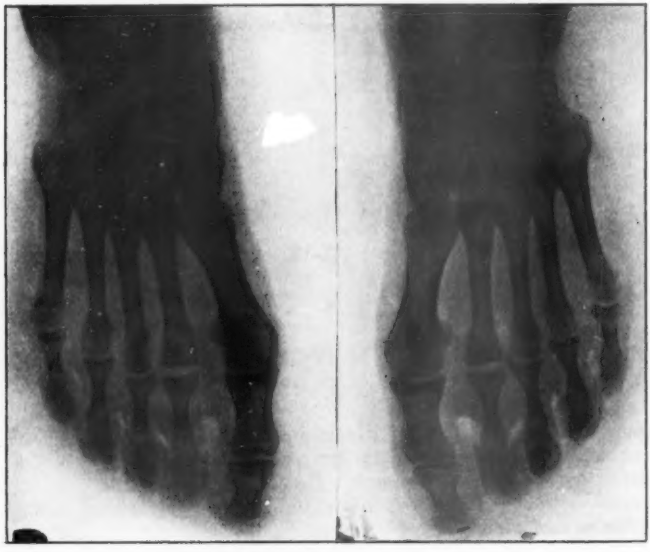
18.2.33 : *Skiagram.*—Left foot : condition had progressed. Right foot normal.

6.4.34 : Commenced to have pain in the right foot.



18.2.33.

FIG. 1.—Showing normal head of second right metatarsal, and flattened head of second left metatarsal.



6.4.34.

FIG. 2.—Sixteen months after previous skiagram, showing flattening of head of second metatarsal (bilateral).

Skiagram.—Flattening of head of second left metatarsal, also flattening of head of second right metatarsal.

3.8.34: *Skiagram.*—Condition has progressed in both right and left metatarsal heads.

Patient still complains of occasional pain—there is limitation of movement, with some grating in the second metatarsophalangeal joints. Pain is relieved by support of anterior arches.

The suggested treatment, if the pain continues, is to excise the affected metatarsal heads.

The following cases were also shown:—

(1) Cyst of Internal Semilunar Cartilage. (2) Bone-Block for Drop-Foot.—P. JENNER VERRALL, F.R.C.S.

Cyst of Carpal Scaphoid.—S. A. S. MALKIN, F.R.C.S.Ed.

External Popliteal Palsy with a Tumour in the Anterior Compartment of the Leg.—C. R. BOLAND, F.R.C.S.I.

Mr. MCCRAE AITKEN demonstrated **Various Splints for use in the Treatment of Infantile Paralysis.**

Section of Medicine

President—Sir FARQUHAR BUZZARD, Bart., K.C.V.O., M.D.

[*November* 27, 1934]

DISCUSSION ON THE ÆTIOLOGY AND TREATMENT OF ASTHMA

Sir Humphry Rolleston: The ætiology and treatment of asthma is a vast subject, and in this discussion, as in that by the Section of Therapeutics and Pharmacology in March 1932, it would be advisable to rule out cardiac and renal asthma. But even with this limitation, asthma as an allergic symptom involves consideration of problems within the realms of immunology, biochemistry, psychology, and the balancing of Nature and nurture, or the relative influence of heredity and environmental factors. It is obvious that the introduction, at least, to this discussion must be confined to a few points.

Asthma, in the sense indicated above, is only one of the reactions in the large, and as yet incomplete, group which is commonly spoken of as the allergic diseases or the toxic idiopathies. These include hay fever, paroxysmal rhinorrhœa or allergic coryza, some eczemas, flexural pruritus, urticaria, angioneurotic œdema, intermittent hydrarthrosis, migraine, intestinal spasm imitating appendicitis and gall-bladder disease, mucous colic, and anaphylactic purpura (Schönlein-Henoch disease); one form of epilepsy has been suggested, as has gout with its tendency to be associated with idiosyncrasies, but this view has not received much support. Atophan (cinchophen) poisoning has recently been described as probably allergic in nature, the hepatic necrosis being regarded as perhaps a special form of the Arthus phenomenon (Quick). This obviously requires further confirmation; in that event atophan would, like aspirin and salicylates, be an example of a non-protein antigen.

The word "allergy" was constructed in 1911 by von Pirquet to describe all forms of altered reaction of the organism, whether exaggerated, diminished, or abolished, and therefore included immunity as well as hypersensitiveness. Its use is now practically restricted to hypersensitiveness, and is not employed for the converse condition of absence of sensitivity, such as is shown in the terminal stages of tuberculosis by cutaneous tests; for this the term "anergy" has been introduced, and in this connexion Garrod spoke of "negative idiosyncrasies." The altered clinical reactions in the direction of apathy, so striking in some diseases of another category, such as the endocrine deficiencies of cretinism, myxœdema, and adiposo-genital dystrophy, are not spoken of as allergic or anergic. It would be interesting to hear, in the course of this discussion, of other conditions presenting the converse of asthma and allied disorders.

The causes of the underlying constitutional state, which is often obviously hereditary, probably otherwise latent, in the vast majority of cases, and transmitted on Mendelian lines, are a difficult problem. The constitution or make-up of the body is so dependent on the internal secretions that it is tempting to invoke endocrine abnormalities, and perhaps especially adrenal insufficiency and hyperthyroidism, but such suggestions would meet with clinical inconsistencies such as are presented by the comparative, though not absolute, freedom from allergic manifestations in Addison's and Graves's diseases. Burn, however, contended that the allergic state, and asthma in particular, are due to a deficiency in the amount of adrenaline circulating in the blood and not to the presence of unusual substances. It would thus be easy to fall back on a change in the constancy of the internal environment ("la fixité du milieu intérieur") described by Claude Bernard in 1878 and only in this century recognized as of fundamental importance. But this only raises the further question on what this constancy depends; according to Cannon this

factor is the autonomic system, thus recalling Eppinger and Hess' earlier incrimination of vagotonia.

What is the significance of the association of eosinophilia, hæmic and local, with allergic manifestations? The extensive work on this subject has recently been summarized by Bray. Should it be regarded as a defence-mechanism or as a concomitant reaction? As injection of adrenaline, which so markedly relieves attacks, is said to remove eosinophils from the blood (Falta), it would appear probable that eosinophilia is not a successful defence-mechanism.

The factor responsible for the localization of the manifestations is, among other reasons, interesting from the point of view of prevention. The importance of previous injury in determining cutaneous or bronchial symptoms is probably fully recognized, but an inherent want of resistance may reasonably be taken into account as an adjuvant or as an alternative influence.

Of the numerous methods of treatment, attention may be directed to the physical methods of exercises approved by the Honorary Medical Advisory Committee of the Asthma Research Council under the direction of Dr. A. F. Hurst, who has done so much in this connexion for years, and to Dr. Gilbert Scott's results from "wide-field" X-ray exposures. The question of specific and non-specific desensitization will no doubt receive due consideration. The therapeutic value of Oriel's urinary "proteose" or p- substance, like its specific nature which hardly comes directly within the scope of this discussion, has excited some controversy. Bray has analysed the published results, and since then Savy and Thiers, who regarded its desensitizing effect as specific and employed their own technique of preparation and dilution, obtained, among 47 cases of various allergic conditions, cure in 43 per cent. and considerable improvement in 36 per cent.; in 21 per cent. there was not any benefit.

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Dr. John Freeman: Sir Humphry Rolleston has been quite clear in defining the word "allergy"; it means for him hypersensitiveness, and such a statement (if we bear it well in mind) will be of great help in clearing up the linguistic situation.

If "allergy" means "hypersensitiveness" it must, to begin with, include all anaphylaxy and the Arthusian phenomena as well as such diseases as asthma, &c., which we are discussing to-day and which I have called the "toxic idiopathies" and Coca in New York has called "atopy." Anaphylaxy in its classical manifestations is a disease of animals and is artificially produced by man, and therefore it does not concern us much in medical practice; but some forms of anaphylaxy are discernible in man, and the Arthusian phenomena in particular are now likely to become more prominent in our work, owing to the present custom of giving a series of small toxin-antitoxin doses as a means of immunization. Those are just of the type to produce severe Arthusian reactions whenever a large dose of serum (e.g. antidiphtheritic or antitetanic) is given subsequently—and we may even anticipate some tragedies.

Furthermore, if Sir Humphry Rolleston's definition holds, we must include under allergy all the hypersensitivenesses to the bacteria caused by infection, e.g. sensitiveness to tuberculin shown by tuberculous cases in the von Pirquet and Calmette reactions, &c. All this must be allergy, and indeed is so understood on the Continent. But such hypersensitiveness is mixed up with and is inseparable from

immunity ; therefore we are, I think, forced to include all immune phenomena under "allergy," and the Widal and Wassermann reactions should properly be considered as allergic. If this is so the question that was asked a year or two ago with bated breath—"*Is* rheumatism really allergic?"—loses all point: of course it is allergic because bacterial infection is involved, and the symptoms of rheumatism must be the resultant of this infection and the body's immune reaction against it. Such an extended use of the word "allergy" is philologically correct ; it is what von Pirquet meant when he coined the word to signify an abnormal reaction, and surely the inventor of a word should have some say as to its meaning. As a matter of fact we know that he wanted to include cancer and old age too, but we need not follow him quite so far as that for the moment. The point I wish to make is that we are throwing away the really great advantage of knowing what we are talking about if, in addition to Sir Humphry's clear general meaning of the word "allergy," the word is also used to signify in particular one small group of allergic phenomena, i.e. those spontaneous and hereditary hypersensitiveness such as our subject for to-day—asthma.

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Sir Humphry raised the question of what localizes the toxic idiopathy symptoms, or rather what determines the form which those symptoms will take. It seems to me that we can see pretty clearly at least five factors that must help to determine this point.

The first factor, the one which most obviously determines locality of the symptoms, must be the place of action of the specific protein irritant. Thus we shall get paroxysmal rhinorrhœa and conjunctivitis from any air-borne irritant such as grass-pollen in hay fever; we must get urticaria when the irritant is either pricked into the skin artificially or is bitten or stung into it by an insect; we must naturally get abdominal distress with a tendency to diarrhœa and vomiting from any food sensitization; and so forth.

Secondly we have heredity: certain manifestations, e.g., asthma, tend to run in the family. One may find, for example, a family in which, say, 16 out of 17 members all have hay fever.

Thirdly, trauma may do a good deal to determine any asthma tendency in the blood to precipitate itself at some injured point. This is noticeable with such toxic idiopathies as urticaria and angioneurotic œdema ; and it seems to me almost equally obvious in the way in which e.g., pneumonia or whooping-cough, by damaging the lungs, will change an eczema into pronounced asthma. Being gassed in the War has had the same effect on many patients. I have seen cases in which the determining pneumonia having been confined to one side, the subsequent asthma was also chiefly confined to that side.

Fourthly, nerve stimulation at any point will tend to determine the manifestation to that point: thus a "tickle" in the nose will notoriously promote paroxysmal rhinorrhœa. I think that in this way also chronic bronchitis promotes asthma in the bronchioles.

There is a fifth and psychological way in which a particular toxic idiopathy may be selected by the body. In this respect I stand between the devil and the deep sea because, whereas the non-psychologists will tend to pooh-pooh such a fanciful idea, the psychologists will say that I do not go far enough; also they will probably think that we non-psychologists have no right to dabble with the subject. To the psychologist asthma is an anxiety neurosis, and he may say that the patient, finding insuperable resistance to the conscious expression of his emotions, resorts for the purpose to some psychological function such as breathing, which thus becomes pathological, i.e. asthma. Psychologists would say that the patient would unconsciously select the toxic idiopathy most symbolical of being shut-in or choking spiritually. I will illustrate this with two cases ; one was that of a woman, an earnest Church-worker,

with bad asthma, who showed such marked lack of mental balance that I sent her off to a distinguished psychologist who found that she had suddenly "gone gay," and had taken a lover who then promptly deserted her. "You can well understand," said he, "how the lady's outraged conscience demands asthma as a means of self-expression." Personally I found this difficult, but subsequent events seemed to corroborate it: after a very little treatment for her chronic bronchitis she suddenly determined to go to Jerusalem where the air was so pure that she was sure to be made better.

The second case was that of a man who suddenly began to have bad asthma when abroad in an eastern country, and when challenged about it admitted that there had been an emotional incident just before the first attack; he had knocked down and killed a man and had been put in prison by the rather arbitrary police. His contemplation of the possibility of hanging may well have helped to localize and initiate his symptoms. In neither of these cases was the psychological factor the "sole cause" as some psychologists would like to claim, but I think that we cannot overlook the possibility of a psychological disturbance thus starting one particular type of toxic idiopathy.

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May I take up one last point. The textbooks seem to be full of inaccuracies on the subject of the toxic idiopathies, but there is one which annoys me particularly. They claim that, whereas you may ameliorate, or may even "cure," a definite sensitization (e.g. to horse-scurf or to grass-pollen) by a course of desensitization, yet the diagnostic skin reactions cannot be reduced thereby and therefore the desensitization is only slight. This statement is untrue, though theories are confidently built on it. If desensitization is undertaken in a thorough-going fashion, not only can the patient be relieved of the normal symptoms, but as the desensitization proceeds, the characteristic skin reactions dwindle until they disappear.

Here are two charts to drive home my point. The first (fig. 1) shows a series of the urticarial wheals which were obtained by prick-reaction tests during a course of desensitization for hay fever. The small wheals to the right of the diagram do

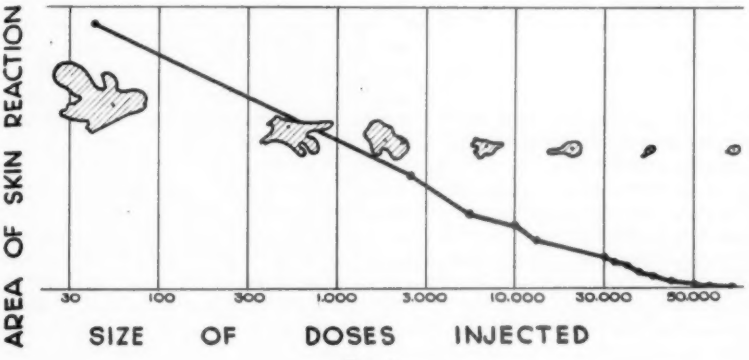

FIG. 1.

not fairly represent the diminution of the reaction, for not only were they smaller in area, but they were so slight in elevation as to make it difficult to outline for reproduction, whereas the large reactions shown to the left of the chart were piled high and could easily be detected by the sense of touch alone. Often such wheals disappear completely, i.e. are indistinguishable from control pricks of normal saline. The curve slanting down from left to right and ending on the base line, or near it,

represents the summation of a number of curves where the area of the urticarial wheal is taken as the index; this tells the same story in another form.

The second chart (fig. 2) shows the result of desensitizing a horse-asthmatic case with horse-scurf vaccine. The continuous line represents the size of the patient's reaction to horse-scurf. The broken line shows her reaction to grass-pollen, for she was also a hay-fever subject though she was not being treated for that complaint. The series of rapidly ascending dots to the left of the chart show the actual inoculations given; it will be noted that they increase from 50 units to 50,000 units in quite a short space of time. Long before the final high dose has been attained the horse-asthma curve begins to flatten out and rapidly dwindles to nothing at all, remaining at or near the base line for as long as the observations were kept up. As a matter of fact the patient remained "cured" for about a year, and when she reappeared for further treatment the sensitization to horse-scurf had only partly returned.

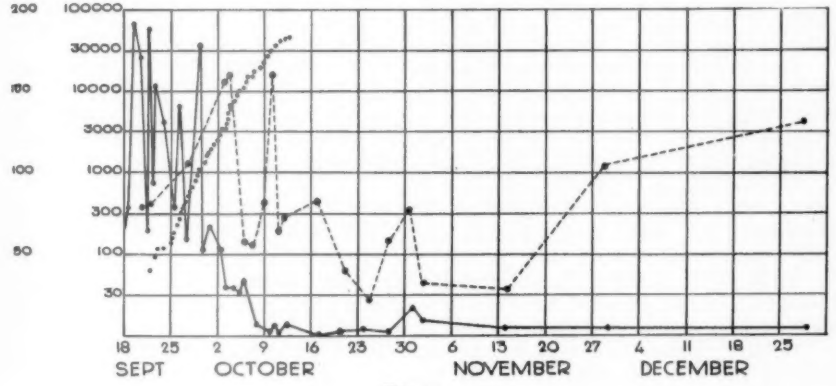

FIG. 2.

It will be observed also that there was a non-specific effect on the pollen sensitization curve from the horse-scurf vaccine; I think it is clear from the chart that the hay-fever tendency, as shown by the broken line, began to diminish also, but it did not diminish so soon, it did not diminish so far, and the improvement was much shorter lived in this non-specific result.

It may be asked why there was this violent fluctuation in the skin reactions at the beginning of the treatment as displayed on the left of the chart. This is, I think, because the skin reactions not only measure the sensitization in the blood to the horse-scurf and the grass-pollen respectively, but being a miniature production of the disease they are measuring also the other factors in the pathological mechanism of the toxic idiopathy, namely, the psychological state of the patient, the liveness of the nerve arcs from the point of skin tested to the central nervous system and back again, and no doubt also such factors as the peculiarities of the piece of skin selected for each test. But it will be admitted that once this thorough desensitization process has taken hold on the patient, all these other factors are quickly wiped out by the almost total reduction of the allergic state.

Dr. James Livingstone said that the two previous speakers had taken a wide view of the allergic diseases, and that he was going to confine his remarks to one small corner of the field, the treatment of asthma by means of breathing exercises. Everyone was aware that asthma was a variable condition, and that individual physicians, with different sorts of treatment, tended to get good results in about 40% of cases. The good results varied more with the personality of the physician, perhaps, than with the special form of treatment he prescribed.

With breathing exercises the patient had a treatment which depended on his own efforts, and not so much on treatment by others. In many cases patients found themselves able to abort, or at least minimize, their asthma attacks by this method, and therefore gained confidence—a most important matter.

The treatment by breathing exercises had three objects in view:—

(1) To get rid of the functional emphysema which was always present, by concentrating on expiration; (2) to increase diaphragm breathing and control, and therefore get rid of the thoracic type of breathing; (3) to mobilize the chest-wall, and to relax the intercostal and other respiratory muscles which were in a state of spasm.

When one examined patients under X-rays, one saw that the diaphragm was taut, and in the full inspiratory position; after treatment by exercises it was sometimes astonishing to see the large excursion of the diaphragm in the chest.

Out of a series of 77 cases of asthma, which had been carefully observed for a period of from one to two years, in 66% the results were good; 16% showed definite improvement; 18% were failures.

[Dr. Livingstone showed some diagrams of the "vital capacities" of certain cases by the Knipping recording spirometer, before and after treatment. In those that had done well, the main change appeared to be the increase in the "reserve" (or supplemental) air, which the patient was able to expire, i.e. the patients who were breathing naturally, with less functional emphysema. The patients who had failed to improve did not show this change.]

As with other forms of treatment in asthma, a great deal depended on the masseuse who taught the exercises; she had to arouse the patients' enthusiasm with regard to the benefit likely to accrue from the treatment, and had to get them to co-operate by persevering and giving up the time necessary to acquire diaphragm breathing. Some patients acquired the knack in a few attendances, whereas others took months, and some were never able to acquire it at all.

He (the speaker) felt that, at any rate, this form of therapy should be given a trial; it was so simple that it could be used with other forms of treatment.

Dr. George Bray said it was agreed, both from clinical evidence and as the result of skin tests, that the majority of asthmatics were sensitive to one or more inhalant substances, such as feathers, animal hairs, house-dust and orris-root. Therefore in any case the avoidance or removal of such specific causes should always be attempted, and every asthmatic should sleep on a rubber mattress and kapok pillows, use orris-root-free cosmetics, and sleep in a room with a minimum of dust-holding surfaces. In desensitizing the patient it was obvious that a mixture of these common inhalant substances should prove more efficacious than any non-specific means, especially if large doses of concentrated solutions were used. For, as in the case of hay fever, positive skin reactions could be abolished if sufficiently strong solutions were used. In the past, weak solutions had been used for fear of constitutional reactions, but nowadays strong solutions could be given without undue fear by adding small amounts of adrenaline to each dose. It might be said that the use of concentrated solutions, buffered with a requisite dose of adrenaline, formed one of the most important recent advances in specific desensitization, and one of the most effective.

Inhalant sensitivity was the most important ætiological factor in asthma at all ages except infancy, and possibly in cases associated with active allergic skin conditions, though even in these latter cases the condition might be maintained by air-borne irritants. In the past too much stress had been laid upon foods and bacteria. Many patients ascribed their symptoms to dietary indiscretions, but specific sensitivity to definite foods was generally a minor factor compared with the lowering of digestive power resulting from a diminished secretion of acid gastric

juice, and chronic gastritis or the reflex effect of gastric distension following large meals causing vagal irritation. By judicious doses of hydrochloric acid and the taking of small, easily digested meals most dietary difficulties could be overcome. Regarding bacteria and their products, there was no definite proof that a true allergic reaction ever occurred from sensitization to their proteins. The only methods known at the moment by which they produced their effects were the local production of histamine in the lungs of a sensitive patient and the local or general lowering of the resistance of the body to some allergen by the infection. In either case the removal of the specific allergen was much more likely to lead to success than was any vaccine treatment. Take the case of the patient who only developed asthma with a cold: if the specific sensitizing substance was determined and removed or the patient desensitized, further colds might arise without the patient developing any asthmatic symptoms. With regard also to nasal abnormalities, recent observations regarded them as merely coincidental or directly secondary to nasal allergic manifestations, so that treatment of such a case should be conservative and non-surgical along allergic lines until all œdema had subsided, when, if the nasal pathology was still deterrent to adequate relief, nasal surgery might be attempted to free the nose from infection and ensure proper drainage and a free airway.

The psychological factor had been stressed, but psychical states could only provoke allergic responses in persons who were already allergic. It was impossible to give a normal person hay fever by getting him to sniff an artificial rose, or even a real one, but in the allergic person, as the result of his allergy to some substance, the symptoms tended to become a conditioned reflex which, after repeated exposures, became capable of being fired off through nervous channels alone without the intervention of the specific sensitizing substance. When, as the result of desensitizing the patient against the primary cause of his reactions, he was shown that he could experience exposure to the original cause without reaction, all the psychical elements disappeared—and especially the factor of expectation—and the case was solely an allergic one.

In summary, specific desensitization, especially to inhalant substances, using concentrated solutions and preventing immediate reactions by the simultaneous injection of adrenaline, was the most practical and successful method of treatment for the great majority of cases of asthma.

Mr. Gill-Carey said that he based his views on the rhinological aspect of asthma on 180 cases, seen during the last ten years, in which full investigations had been carried out.

Rather more than 50% of the patients had allergic changes in the nose and sinuses; in about 10% it was possible to recognize that bacterial infection had been added to the original allergic sinusitis.

Cases fell, roughly, into two groups: (I) Those showing the typical appearances of vasomotor rhinitis; (II) those with non-allergic nasal abnormalities; bacterial sinusitis; septal deviations, and normal noses.

Group I.—Allergic rhinitis accounted for more than 50% of the cases. The typical colour changes of allergic œdema were unmistakable. In many mucous polypi and radiological evidence of thickening of the lining membrane of the sinuses were present. Surgical abuses had been most frequent in this group, partly on account of a failure to recognize that the changes present were not due to infection, and partly to the fact that temporary improvement was nearly always produced by radical sinus surgery.

In cases without infection, rhinological treatment was secondary to other means of attack, and consisted mainly in keeping the ethmoid area free from polypi causing obstruction and perhaps reflex irritation.

In the group in which allergic changes were combined with chronic infection, active rhinological treatment was beneficial. Those cases in which the addition of infection to an allergic sinusitis had coincided with the onset of asthma were most

likely to give satisfactory results. Improvement in general health resulted from the successful treatment of the septic element in this group.

Group II.—The second group of non-allergic nasal abnormalities would vary in size with the standards set by the individual observer. In this series it accounted for about 10% of the cases. The most satisfactory results in this group were obtained by the treatment of sinusitis.

Except in those cases in which correction of a deviated septum was a part of the treatment of sinusitis, no permanent improvement with regard to the asthma was noted. On the other hand, if the operation was limited to cases with gross deflections the increase in nasal comfort was appreciated.

The temptation to attack the inviting masses of hypertrophic tissue in the pure allergic sinusitis must be withstood; on the other hand, the appropriate rhinological treatment would, in selected cases, give satisfactory, and at times brilliant, results.

Professor Ernest M. Fraenkel: The constitutional behaviour of the patient is at least of the same importance as the external cause—the allergens. Both factors vary in different patients, and even in the same patient at various stages of the disease. The protection from allergen is thus only one side of the question. It is nevertheless useful for a large proportion of the patients for diagnostic, prophylactic, and therapeutic purposes.

The film entitled "Allergy and Allergic Diseases" shows experiments with anaphylactic shock in guinea-pigs both with the guinea-pig itself and by making use of the "Dale test." It further demonstrates various allergens and the construction of filter apparatus, which afford protection from the allergens in the air. Finally, the protection of a patient with dog's-hair asthma is shown, when exposed to the specific allergen, while wearing a mask.

When, without the patient's knowledge, the filter has been removed and an empty filter box substituted, the patient has a severe attack of sneezing, conjunctivitis and asthma.

The mask can thus be used in diagnosis for the exclusion of psychological factors. We can further determine the site of entry by protecting either the mouth, nose, or conjunctiva with the mask, or the whole body, using a filter-sleeping-bag or an allergen-free room.

By the use of various filter-media a certain inference may be made as to the nature and size of the allergen.

The mask enables some patients with a professional hypersensitivity to continue working in the presence of specific allergens, so being used for prophylaxis. In other cases the use of the mask for a part of the day (during the night when asleep) will prevent the onset of attacks.

For therapeutic purposes the mask should not be used when first treating untrained patients in an acute stage of the attack. We recommend first the use of the allergen-free room and subsequent training in the use of the mask. Some patients obtain relief only when wearing the mask, others when using the mask during the night. A third group loses the attacks for a period of weeks or months after a period of two or three weeks of treatment.

In two tables, 522 asthma cases were analysed from the point of view of allergic conditions. The skin tests showed that inhaled allergens (house allergens) were prevalent. Another picture shows a new design for the adaptation of filters and sliding doors and windows to ordinary rooms in hospitals and premises which could thus be easily transformed into allergen-free rooms.

Sir James Dundas-Grant laid great emphasis on the importance of the nasal element in spasmodic asthma. When the vago-accessory centre was over-sensitive, owing to some cause—dietetic, hereditary, psychical, or other—an irritant in the nose was frequently the determinant element in the reflex contraction of the bronchiolar muscle. When a distinguished laryngologist, who had joined up early in

the War, lamented on his return that his practice had quite gone, a friend—a respected physician—had assured him that if he resected a few deflected septums for asthmatic patients he would soon recover his practice.

The frequency of nasal abnormalities in the subjects of asthma was considerable and out of 107 cases referred to him (Sir James) there were, in 68, nasal changes so well-marked as to call for—or at least justify—operation, such as enlargement of middle turbinated bodies, hypertrophy of the anterior lip of the hiatus semilunaris, deflection of the septum—especially of its upper part—polypi or polypoid outgrowths and sinus suppuration. Disappearance or mitigation of the asthmatic attacks after removal of nasal disease was frequently observed, as in 33 cases of practical cure and 67 of improvement, out of 120 comparatively unselected cases. In children with asthma continuing in spite of removal of tonsils and adenoids and resisting general treatment, great enlargement of the middle turbinals was sometimes present. When he (Sir James) had shown a case at the Clinical Section[1] of a cure of asthma in a child by removal of a hypertrophied portion of the middle turbinal, he had been asked by the President in how many cases the operative treatment had failed to give relief. He investigated his notes and found that out of 18 consecutive cases, 15 had complete relief and 3 improvement. Recrudescence of the asthma was also observed to follow return of the nasal disease. Dixon, Brodie, and Ransom's experiments demonstrated the presence of asthmogenic areas in the nose, especially the upper and back part of the septum. Disappearance of sensitiveness to specific or other irritants was scarcely to be anticipated as a result of nasal operation, but in at least two cases he (the speaker) had observed it, in one for cat emanation and in another for ingestion of cake or nuts when, after operation, the former could handle cats and the other indulge in cake and nuts without the occurrence of asthma. It was essential to combat the causes of the vagal hypersensitiveness, as so ably set forth by previous speakers, and he looked upon this as the "explosive" while the nasal irritation was the "detonator." He insisted, therefore, on the removal of the "explosive," if possible, but otherwise the removal of the "detonator."

Dr. F. Parkes Weber referred to various factors which could lessen or depress the allergic reaction in admittedly allergic diseases, such as asthma, allergic diseases of the skin, &c. He would not allude to the regular methods of desensitization. The allergic reaction in asthma could, of course, often be lessened or overcome by injections of adrenalin. In hospitals one often met with cases of *acute generalized dermatitis* in vigorous individuals, which were obviously allergic in nature, though the actual exciting cause, acting through the alimentary canal ("allergen" if one might call it so), could not be discovered. With rest in bed such patients usually gradually recovered, but they recovered more rapidly if they were put on a semi-starvation diet (of milk, &c.) for a few days. There were two obvious explanations for this, one or both of which might be correct: (1) The simple low diet removed, or rather, was free from, the exciting cause ("allergen"); (2) the relative starvation itself might be useful (and Dr. Weber thought it was) by reducing the allergic reaction in these cases, as the administration of adrenaline did in cases of asthma.[2]

Could the withdrawal of blood ever lower allergic reactions like partial starvation apparently did in some cases? Perhaps in former times bleeding for so-called "sthenic" pneumonia in robust individuals acted in this way, by lowering the allergic reaction towards the microbic agents of the disease—an allergic reaction that sometimes threatened, so to say, to "choke" the patient.

Dr. James Adam, basing his remarks on an experience of 1,600 cases, emphasized the importance, in asthma, of the nurtural factor, with resultant toxicosis. Proof of this was shown in :—

1 *Proceedings*, 1930, xxiii, 947 (Clin. Sect., 63).

2 The same question crops up in regard to the beneficial effect (on some asthmatics) of high altitude climates in Switzerland: Is it due to relative absence of allergens, or to diminution of the patient's allergic reaction, or to both factors?

(1) The occurrence of asthma in lower animals kept as pets or in unnatural conditions (canaries, dogs, pit ponies, &c.) and their improvement with attention to diet and exercise.

(2) The frequency of asthma in "only" and other pampered children, with improvement under a more Spartan life.

(3) The rarity or absence of asthma among the Eskimos and Red Indians, who had to hunt for their food before they ate it.

(4) The prevalence of week-end asthma among working folk owing to the under-exercise and overfeeding of the week-end; its mitigation by the reversal of these showing that adrenal fatigue or the week-end bath were not feasible explanations.

(5) The disappearance of asthma and other allergic symptoms in many soldiers during the strenuous life of the War, and its reappearance on return to the laxer conditions of civil life.

(6) Low alkali reserve before and during an attack, with rise of this reserve and lower eosinophil count and absence of wheeze on detoxication.

(7) Recurrence of wheeze and increase of eosinophils if urea, a waste product harmless to normal people, was ingested by asthmatics while they are improving but before detoxication is complete.

(8) The contrary, after regular use of a potent intestinal antiseptic such as a mercurial, or sometimes after thorough colonic douching or with fasting and abundant water drinking.

This conception of a toxicosis depressing enzymatic activity throughout the body would explain the hypochlorhydria, impaired liver, adrenal, and thyroid function, and the cachexia found in chronic asthma; it also explained the value of adrenaline and iodides.

In reply to Sir Humphry Rolleston: adrenaline lowered the eosinophil count but a cold douche after a warm bath was even more effective by its prolonged stimulation of the adrenals through the sympathetic. The eosinophil cells were probably to be regarded as scavengers rather than as soldiers.

Dr. Clement Francis said that there were two measures connected with the nose which were of particular interest in regard to asthma. Rhinologists were familiar with the fact that operative removal of nasal polypi produced widely different results in apparently similar cases of asthma. In his experience no extensive operation for the removal of nasal polypi should be performed in an aspirin-sensitive asthmatic with a low systolic blood-pressure, for such a procedure usually increased the asthma. Polypi could, however, be removed in other asthmatic cases with advantage.

The second measure was light cauterization of the nasal septum. This produced permanent benefit in patients with a healthy nose. In contradiction to some opinions, he believed that the improvement with regard to the asthma was due, not to removal of sensitive areas in the nose, but to a stabilizing effect on the vasomotor system, for it was his experience that the lighter the application, the better was the result. An interesting fact illustrating the effect produced by this means on the circulation was the reduction in systolic blood-pressure which followed the application of the cautery in cases in which the blood-pressure was above the average.

Asthma was largely a question of vasomotor stability, and any measures to improve the circulation would undoubtedly diminish the asthma, whatever the allergic reactions of the particular case might be. Thus moderate exercise and massage were valuable. Patients who, when exposed to cold night air after sitting indoors, habitually developed asthma, found that they did not get an attack when going out at night after steady exercise, such as dancing, because in this case their circulation was sufficiently improved for the time being to enable them to withstand changes in temperature. Some people found that they could abort a threatened attack of asthma by massaging the hands and wrists if these were cold.

Section of Comparative Medicine

President—J. B. Buxton, F.R.C.V.S.

[*October* 24, 1934]

Some Aspects of the Rôle of Tuberculin in the Control of Tuberculosis

PRESIDENT'S ADDRESS

By J. Basil Buxton, F.R.C.V.S.

Definition of tuberculin.—The term "tuberculin" has been applied not only to the glycerinated extract originally obtained by Koch, but also to a very large number of analogous substances prepared from cultures of the organism by Koch himself and by other investigators using several procedures. These "tuberculins" may be grouped roughly into two main classes: (1) The products of growth of the organism either in crude filtrates or obtained by refining processes; (2) suspensions of tubercle bacilli or the products of their disintegration obtained by physical or chemical means.

For the purpose of this dissertation the term "tuberculin" will be limited to indicate, as in the Therapeutic Substances Act, "preparations of fluid media on which the *Bacillus tuberculosis* has been grown in artificial culture and which have been freed by filtration from the bacilli."

The tuberculin reaction.—The tuberculin reaction is now generally accepted as a phenomenon of hypersensitivity (allergy) due to the sensitization of the body-tissues to the products of growth of the tubercle bacillus. It may be either general (systemic) or local, according to the way in which tuberculin is applied to the tissues of responsive individuals. In the former case the tuberculin produces a local lesion at the site of injection, a focal lesion at the site of tubercles in the tissues, and a constitutional reaction, consisting of fever and the accompanying general symptoms of intoxication, which in severe cases may result in death.

It is also accepted that the reaction elicited by the application of tuberculin to the tissues of a tuberculous subject is brought about by certain protein fractions of the tuberculin. Such fractions have been obtained by various workers since the time of Koch, but it was not until comparatively recently than an active protein has been isolated. Seibert (1927, 1928) reported the isolation of a water-soluble coagulable protein in crystalline form, obtained from the growth of tubercle bacilli in a protein-free synthetic medium. She has since suggested (Seibert and Mundy, 1931) that a specific portion of the protein molecule which is present in the early cleavage products obtained during hydrolysis is responsible for the skin reaction.

Specificity of the tuberculin reaction.—Experience has established the highly specific nature of the tuberculin reaction. It is recognized, of course, that every case of tuberculosis, either in man or in lower animals, will not necessarily give a positive reaction to tuberculin, and, conversely, positive reactions are occasionally observed in apparently healthy persons and cattle, but from innumerable records of autopsies immediately following tuberculin tests in man and, of course especially, in

lower animals, it has been shown that when carefully applied, tuberculin is capable of indicating the presence of tuberculous infection in little short of 100% of infected individuals.

The importance to be attached to this revelation of tuberculous infection varies enormously according to our interpretation of its significance in human beings and in animals under widely differing circumstances.

Diagnostic applications of tuberculin.—Many methods have been devised for the diagnostic use of tuberculin, but only a few have withstood the test of time and are now employed extensively in man and lower animals.

The subcutaneous method, which was the original method of Koch (1890, 1891) causes local, focal, and general reactions in man and animals. Since the danger resulting from focal and general reactions far outweighs the value of positive evidence of infection, the method is now only used to a very limited extent in man.

In cattle, on the other hand, it was, until comparatively recently, the most extensively used test in this and in certain continental countries but has been almost entirely superseded for official purposes in those countries in which a serious attempt has been made to control tuberculosis in cattle.

The Medical Research Council Tuberculin Committee (1925) stated:—

> "The subcutaneous tuberculin test appears to be a perfectly satisfactory test for the presence of tuberculosis in cattle, when carried out under the laboratory conditions of a scientific trial. It is not a satisfactory test when carried out under ordinary farm conditions; the discrepancies then prevailing are often so numerous as to vitiate the general application of the test for practical purposes."

Further, the test must be regarded as unsatisfactory for official purposes in any scheme to eradicate tuberculosis in cattle, if for no other reason than by virtue of the fact that tuberculous cattle can be rendered incapable of reacting to the test by the previous injection of suitable doses of tuberculin. To overcome this difficulty, when there has been *reason to suspect* that animals have received a subcutaneous injection of tuberculin within a short time before the test, a larger dose of tuberculin —up to five times the amount usually employed has been used. If such information is available, and this is by no means always the case, this precaution may overcome the difficulty in some instances. It has been recognized for a long time that "doping" or "plugging" with tuberculin may vitiate a subsequent subcutaneous test, and advantage has not infrequently been taken of this knowledge by unscrupulous persons to get an animal which they know, or suspect, to be tuberculous to "pass" the test. But it is not sufficiently well recognized that unintentional "doping" in the form of intensive testing by the subcutaneous route may lead to a desensitization of some of the animals, so that herds have come to be regarded as free from tuberculosis as judged by this test, when, in fact, they contained a number of tuberculous animals. Another disadvantage of the test in cattle lies in the fact that on account of the focal reaction which it produces, infected animals, and especially those which have tuberculous foci in the udder, may, as a result of the reaction extrude relatively heavy contaminations of tubercle bacilli in their milk. Indeed advantage is sometimes taken of this fact and tuberculin is injected subcutaneously in order to facilitate a positive diagnosis in examinations of the milk from udders which are suspected of containing tuberculous foci. I need not labour the point; sufficient has been said to show that, if for no other reasons than those I have given, the subcutaneous method cannot be regarded as a satisfactory test for cattle.

The ophthalmo-reaction, or conjunctival tuberculin test of Wolff-Eisner (1908) and Calmette (1907) has been discarded for use in man, owing to the severity of the reactions which it sometimes produces. In cattle the test is still employed, but to a limited extent. The tuberculin used is either crude old tuberculin or a purified preparation obtained from it. In practice the test has not proved sufficiently reliable

to warrant its use alone. It is, however, used occasionally in conjunction with some other method.

The cutaneous method of von Pirquet (1907) and the *intracutaneous method* of Mantoux (1910) are the only widely used tuberculin tests in man at the present time. It has been claimed in the case of the former, that a primary positive reaction suggests the existence of a comparatively recent lesion, while a torpid or secondary reaction indicates the presence of an old lesion in the process of healing. It is, however, generally agreed that a positive reaction indicates a state of allergy due to a sometime tuberculous infection but does not differentiate an active lesion from an infection which is quiescent or overcome. Several modifications of von Pirquet's original technique have been introduced, especially with a view to obtaining quantitative results by means of geometrically progressive dilutions of tuberculin, and thereby deducing the state of the lesions.

Both methods are extensively employed in human medicine and each has its staunch supporters. An excellent summary of reported work has been made by D'Arcy Hart (1932 [2]) and his conclusions, based upon his own work and that of others, show that, when care is taken in the application of the method and in interpreting the results, the intracutaneous test is the most satisfactory tuberculin test in man.

In cattle, tests of the von Pirquet type are impracticable as a routine measure. In white-skinned animals it is possible to detect some degree of erythema, but on account of the comparative thickness of the skin and of the much lower degree of sensitiveness of tuberculous cattle to tuberculin, compared with man and guinea-pigs, it is almost impossible to assess the result of these tests with any degree of precision.

The intradermal reaction may be obtained on any part of the surface of the body, but certain regions are obviously to be preferred. Mousau and Mantoux suggested the subcaudal fold in cattle and this site is still used extensively, especially in the United States of America while others (Ligniéres, Roemer and Joseph, Bang, Jensen, Christiansen) preferred the side of the neck. Joseph (1909) gave a full account of the test in the neck and recorded the results in cattle, based upon measurements of the skin-fold at the site of the injection.

The Tuberculin Committee of the Medical Research Council (1925) recommended a modification of the technique employed by earlier workers. Briefly the test consists of the introduction of 0·1 c.c of concentrated tuberculin into the deeper layers of a measured fold of skin. At the 48th hour, a positive response in the form of an œdematous swelling may have resulted, but if the reaction is in the nature of a hard, circumscribed and painless swelling which characterizes a negative reaction, a second dose, also of 0·1 c.c. of tuberculin, is injected into the centre of the swelling. In animals which are not sufficiently sensitive to react to a single dose of tuberculin, the first inoculation serves the purpose of sensitizing a limited area of skin to the second dose.

Tuberculin sensitiveness in cattle.—The extensive use of intracutaneous tuberculin tests on cattle has raised several points of interest in connexion with the capacity of these animals to react to tuberculin applied in this manner.

While there is no reason to believe that there are any significant differences in the qualitative results of the intradermal test in the various species susceptible to tuberculous infection, there are marked variations in the degree and character of the skin-sensitiveness.

The relatively large doses of tuberculin that are necessary in applying the test to cattle are in marked contrast to the much smaller amounts that are capable of revealing specific sensitiveness in man or in the guinea-pig. Although this difference may depend to some extent upon the relative thickness of the bovine skin, it is unlikely that this is entirely responsible for the lower degree of sensitiveness in cattle

and it is reasonable to suppose that the cutaneous tissues in the bovine subject are less responsive than are those of the other species. Whereas in man, cutaneous reactions can frequently be obtained with dilutions of 1 : 1,000 and even up to 1 : 10,000, and similar responses can be obtained in guinea-pigs at a certain stage of tuberculous infection (Eagleton and Baxter, 1923; Okell, 1929), in cattle it is necessary to employ concentrated tuberculin as a routine procedure. While it is true that definite positive reactions may be obtained with 0·01 c.c. and even with 0·001 c.c. of "O.T." and that in animals which are highly allergic, reactions of a gross character may result from the injection of the usual dose (0·1 c.c.) of the concentrated product, it is certain that in the majority of cattle the sensitiveness is of a much lower order. In the course of an ordinary tuberculin test in an infected herd of cattle, the response to a dose of 0·1 c.c. of concentrated tuberculin is, on the average, of a moderate intensity; moreover, while some indication of a reaction may be given to the first dose, it is necessary, in a proportion of the animals, to follow this with the second dose in order to obtain a definite result from the test. Experience has shown that in many of these instances the animals are in an advanced stage of the disease and their detection is therefore of the greatest importance.

The nature of the non-specific reaction.—In the human subject, the term "non-specific reaction" is generally applied to the positive type of response to a non-specific reagent, such as glycerine-veal-broth, when it occurs in a tuberculous subject. In referring to non-specific reactions in cattle we use the term in a slightly different sense as indicating a reaction in *non-tuberculous* animals to either tuberculin or concentrated glycerine-veal-broth and reserve the term pseudo-positive reaction for non-specific responses in the *tuberculous* subject. The injection of 0·1 c.c. of tuberculin or of the same amount of concentrated veal broth into the skin of non-tuberculous cattle gives rise to a hard, circumscribed, painless swelling about the size of a pea or a bean. It is evident therefore that there is a basic reaction of the tissue to some constituent common to both products which is designated the non-specific reaction. In the human subject, Willis (1932) has reported that a solution of 50% of glycerine in distilled water or normal saline solution produced in non-tuberculous persons a distinct nodular swelling that persisted for four or five days and might have been mistaken for a positive reaction to tuberculin. In the guinea-pig pseudo-positive reactions have been observed with as low a proportion of glycerine as 5% (Allen, 1931). On the other hand, D'Arcy Hart (1932[1]), in the course of a careful inquiry into the specificity of skin-reactions in man, examined the different constituents of concentrated glycerine broth with reference to their power of inducing reactions in the human skin. He found that glycerine was not responsible for the production of non-specific responses, even when employed in a concentration of 50% (5% glycerine evaporated to one-tenth of its volume), but of the other substances contained in the broth, both the peptone and the veal extract were capable of eliciting skin-reactions, although comparatively large amounts were required.

A study of the various components of glycerine-veal-broth in respect of their power of eliciting a non-specific dermal response in calves has shown that no appreciable reaction results from the injection of mixtures of glycerine with saline solution or broth in proportions as high as 50%, or with a one-per-cent. veal infusion, with or without peptone, concentrated to one-tenth of its volume (Glover, 1933). In other words, each of the ingredients of concentrated glycerine-veal-peptone-broth is incapable, by itself, of producing the non-specific type of reaction. When, however, a glycerine-peptone-veal broth is reduced to one-tenth of its volume by evaporation, it would seem that a substance is elaborated which is responsible for the bean-like swelling. It is believed that this substance, which is also present in "O.T.," is elaborated by the action of the glycerine on the protein components during the process of evaporation.

The comparatively low order of the skin-response to tuberculin in the case of cattle necessitates the use of a highly potent tuberculin in these animals. Koch's

"O.T." meets this requirement, but raises some difficulty in differentiating the reactions just described from those of the slight diffuse positive type. In the hands of one who is expert in applying and interpreting these tests, little difficulty is experienced, but inasmuch as most of the routine testing of cattle has to be undertaken by veterinary surgeons who are not continuously engaged in the work, and who therefore have less opportunity of observing and appreciating such minute details, it is of advantage to use a control fluid consisting of concentrated glycerine-veal-peptone-broth for purposes of comparison.

The difficulty can, however, best be overcome by the use of tuberculin consisting of a solution of tuberculo-protein obtained by the precipitation of the active principle from a synthetic medium in which the tubercle bacillus has been grown. We have shown (Buxton and Glover, 1932-33) that a simple extraction with ammonium sulphate, followed by solution of the precipitate in a mixture of glycerine and tap-water, provides a form of tuberculin which is very suitable for the testing of cattle by this method.

With this preparation there is an almost entire absence of response in the non-tuberculous animal, while in tuberculous cattle the reactions are equal in intensity to those induced by a comparable dose of "O.T."

In this connexion the possibility of sensitization to tuberculo-protein requires consideration. Numerous attempts have been made to sensitize animals by repeated injections of "O.T.", but since these efforts have been uniformly unsuccessful, it is unlikely that non-specific reactions to old tuberculin can occur in cattle. In the case of purified forms of tuberculin Seibert (1933) has shown that repeated injections of unheated purified tuberculo-protein were capable of inducing a specific cutaneous sensitization to the homologous antigen and that this response simulated an ordinary tuberculin reaction in a tuberculous subject. She believes that modification of the protein by heat has accounted for previous failures to elicit phenomena of the Arthus type. Aronson and Nicholas (1933) have shown that the intradermal inoculation of an unheated purified tuberculin (M.A. 100) in the human subject may lead to sensitization in a certain number of individuals when re-tested on a subsequent occasion. These results have been confirmed by other workers and show quite clearly that under certain circumstances undenatured tuberculo-protein may induce a state of hypersensitiveness to itself. Experiments carried out by R. E. Glover, at Cambridge, on the effects of the parenteral introduction of unheated tuberculo-protein have shown that allergy may be produced in the guinea-pig so that it gives a skin reaction which exactly resembles a positive tuberculin reaction, whereas no reactions were produced in guinea-pigs which had received *heated* tuberculo-protein. It would seem, therefore, that heat, probably by altering the nature of the specific protein, removes from tuberculin the power of sensitizing the skin.

The fact that the precipitated synthetic medium tuberculins which we have prepared have been steamed for two hours previous to precipitation should remove any risk of their being capable of sensitizing the subjects to tuberculin. Experiments on calves have confirmed this supposition. A number of non-tuberculous animals have been repeatedly tested intradermally with a heated precipitated synthetic medium tuberculin, several injections being made at different sites in the skin of the neck. The amounts of this tuberculin introduced have varied from 0·2 c.c. to 1·6 c.c. and the intervals between the injections from 3-4 weeks up to 9 months. At no time has there been any evidence of sensitization by the tuberculo-protein to subsequent injections of the same product (Buxton and Glover, 1933).

Fluctuations in sensitiveness.—In the course of routine tuberculin-testing, concentrated glycerine-veal-broth is often used as a control measure, and in this capacity is of considerable help in facilitating the differentiation of negative

reactions and those which exhibit a very slightly œdematous appearance and are properly classified as positive reactions. It has been found, however, that, on rare occasions when the two substances have been used simultaneously on a reacting animal, the concentrated glycerine broth has induced a reaction resembling a positive tuberculin reaction by reason of the presence of some œdema. Reactions of a similar nature have been observed in man and in other species. D'Arcy Hart (1932[2]) has shown that, whereas individuals who are negative to a 1 : 1,000 dilution of tuberculin almost invariably give a typically negative response to concentrated glycerine-broth, many patients who are markedly tuberculin-positive possess a sensitiveness for the broth.

In the case of cattle, an inquiry into those instances in which the glycerine broth has appeared to give a pseudo-positive response, has usually elicited the information that, firstly, the two products were injected in close proximity on the same side of the neck, and secondly, that the reaction to the tuberculin was very marked. Pseudo-positive reactions to glycerine broth have not been observed in those subjects in which the tuberculin reaction has assumed the form of a slightly diffuse swelling. This phenomenon seems to suggest that under certain circumstances, a local non-specific sensitiveness to glycerine-veal-broth may sometimes arise in the highly allergic animal. Glover has found that in cattle this type of sensitiveness is purely a local reaction. By selecting animals with a high and a low allergic reaction to tuberculin at a given point on one side of the neck, and then making a series of inoculations of concentrated glycerine-broth at varying distances from it he was able to show that in animals in which the allergic response was slight, the swellings induced by the glycerine broth were invariably hard and circumscribed, irrespective of their distance from the tuberculin swelling. On the other hand, in animals showing a large œdematous reaction (25-35 mm.) to the tuberculin, the injections of glycerine broth at distances of from 3 in. to 6 in. sometimes acquired a pseudo-positive character, while similar injections on the opposite side of the neck were definitely negative. It is evident, therefore, that pseudo-positive sensitization in such instances is restricted to an area of the skin in close proximity to the tuberculin reaction, and is also closely related to the allergic state of the animal. These observations are in accordance with accepted views on cutaneous reactivity in tuberculin sensitive subjects to various non-specific protein substances (Tytler, 1930).

Conversely it has been shown that in laboratory animals the skin can be desensitized by a series of increasing doses of tuberculin given by the subcutaneous route (Boquet, 1932), but there is no indication that the intradermal injection of tuberculin will bring about the same result. Recent experiments by Boquet and Valtis (1933) suggest that in guinea-pigs the responsiveness of the skin is not influenced by previous injections of tuberculin, since they found that the injection of tuberculin into a previous site induced a response which was equal in intensity to the reactions at other points of the skin. There seemed, therefore, to be no evidence of a local desensitization.

In cattle, one of the advantages claimed for the double intradermal test is that it is reliable on repetition. Experiments which I carried out (Buxton and MacNalty, 1928) showed that cattle receiving repeated large doses of tuberculin by the subcutaneous route, continued to give marked reactions to the double intradermal test. Further, the repeated application of the intradermal test at short intervals showed no evidence of a cutaneous desensitization, since the intensity of the reactions to succeeding injections of tuberculin was not diminished. In these tests, however, a fresh situation was chosen for each inoculation. We have since shown that, just as localized areas of hypersensitiveness may be induced, so areas of diminished sensitiveness may arise, and we have obtained evidence that an

intradermal injection of tuberculin may result in a temporary decrease in the allergic reaction of the tissue in the immediate vicinity. In these experiments calves which had reacted to a single intradermal injection of tuberculin were re-tested at varying intervals, both at the site of the original injection and also at selected points at increasing distances from it. In several instances it was found that the original site, together with an area of about 2 inches in radius around it, was markedly less sensitive to the second injection, whereas the more remote injections produced an intensity of reaction equal to a control-injection on the opposite side of the neck. It is evident, therefore, that care should be exercised in selecting the area of skin to be used for intradermal tests and that, if there is any reason for supposing that a previous injection has been made at that site, it should be avoided. This observation suggests that the use of the subcaudal fold in cattle as a suitable site for repeated injections with tuberculin, has definite limitations, owing to the restricted area which is available for the purpose.

The ultimate rôle of tuberculin in the control of tuberculosis in man or in cattle cannot be definitely forecast in the light of our present knowledge. Unremitting attempts to acquire a fuller understanding of the limitations of the tests have done much to increase the intelligent use of tuberculin and the interpretation of the real significance of possible implications revealed by its use.

The comparative delicacy of the sensitiveness of the human skin, in conjunction with greater facilities for accurate clinical diagnosis, renders feasible much wider interpretations of positive reactions in man than can be hoped for in the case of cattle, for—while in the latter we can still only say that a positive reaction to tuberculin means essentially that the reacting animal has at some time been infected by the tubercle bacillus, and, in the absence of gross clinical symptoms, nothing more—in man there is hope, that with further experience it may yet be possible to differentiate the allergic response in cases of quiescent tuberculosis from that exhibited by active forms of the disease. Such a differentiation, if it can be established, will play an enormous part in determining not only the relationship of immunity to susceptibility but also the conditions under which infection protects against, rather than produces, active disease.

In man, also, it must play a highly important part in an epidemiological survey of the disease, by assisting to establish such important considerations as the relative significance of heredity and contagion in non-bovine tuberculosis both in children and adults, not merely as regards the inheritance of a predisposition to infection but also in respect of the relationship of hereditary factors to post-infectional development. Again improvements in and standardization of the technique employed, have rendered possible the determination and correlation of factors concerned with the epidemiological study of the disease in relation to environmental and occupational conditions.

The next few years should see a marked development of measures based upon the use of tuberculin in the control of tuberculosis in man.

In the case of cattle-tuberculosis, the position is rather different but, in its way, not less important. Any attempt to control the incidence of the disease, based upon voluntary measures, will stand or fall according to the results of tuberculin-testing on a large scale.

Continuous attempts have been made over a number of years to acquire a working knowledge of the many difficulties which are likely to be met with under the conditions of extensive testing in this country.

Experience has been gained from the study of repeated tuberculin tests in herds under the Milk (Special Designations) Order, and as a result it is no exaggeration to say that, standing, as we hope we are, on the threshold of a new era of tuberculosis control in cattle, we are far better equipped for the struggle than was the case even

a few years ago. I do not mean to suggest that there is no room for improvement; that must come with the development of a standardized technique and a better understanding derived from our further experience.

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Section of Obstetrics and Gynæcology

President—EARDLEY HOLLAND, F.R.C.S.

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Further Studies in Adult Rickets (Osteomalacia) and Fœtal Rickets

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NOTE.—This paper would have been impossible without the cordial coöperation and help of my colleagues in the Peiping Union Medical College who have allowed me to use the results of their work and have given me advice in various directions. My thanks are especially due to Dr. R. R. Hannon and Dr. S. H. Liu of the Department of Medicine; Dr. A. P. Black of the Division of Pediatrics; Dr. C. H. Hu and his colleagues of the Department of Pathology; Dr. C. K. Hsieh and his colleagues of the Department of Radiology; Drs. Miltner and Meng of the Division of Orthopædics; Miss Sophie Chen of the Dietetic Division, and the members, both doctors and nurses, of my own Staff. My thanks are also due to Mr. Wang for photographs and microphotographs, whilst Dr. Wolfe has made a special study of the teeth in cases of fœtal rickets. My thanks are also due to Professor H. M. Turnbull for his valuable advice.

OWING to the difficulty of obtaining autopsy permits in China at the present time, it has hitherto been impossible to obtain the tangible evidence of osteomalacia necessary to complete the demonstration of the Chinese cases, but one is now able to present the evidence afforded by specimens from two patients.

Through the kindness and enterprise of Dr. Wagner of Taiku, Shansi, a perfect specimen of a pelvis from a case of advanced osteomalacia was obtained, and he also supplied the notes of the case. (This pelvis is now in the Hunterian Museum of the Royal College of Surgeons.)

This is the first specimen of an osteomalacic pelvis obtained from China. It will be called the Shansi pelvis. In previous papers by the writer [1, 24] it has been pointed out that Shansi is one of the centres in which the disease is exhibited in its worst form.

Mrs. K. (fig. 1), aged 39, entered hospital when five months pregnant. She was of pure Chinese descent, and had lived all her life within a radius of a few miles from her birthplace. One sister-in-law had osteomalacia. She had no serious illnesses as a child, or in early married life. Beginning one month after the birth of her second child, fifteen years before admission to hospital, she began to suffer from pains in the arms, legs and lower part of the back. Three or four years later she noticed that her back was bending. Eight years ago she began to take cod-liver oil and took it for two years. For the last seven years her deformity had remained constant. She had been free of pain for the past three years. She was a slight short woman, with a marked kyphosis, bending forward at the hips so that she walked with the trunk almost horizontal, the head being raised as far as possible, so that the eyes could just see straight ahead. She walked with two canes, and moved very slowly with short steps. The left costal margin overlapped the iliac crest, the right costal margin approached to within two fingerbreadths of the iliac crest. Although there was a heavy fold of abdominal wall there, the abdominal contents did not distend it. The umbilicus was hidden in an inverted crease which sagged as an empty patulous fold in front of the symphysis.

The symphysis presented a broad face which looked upward and forward, and its superior margin was 3·5 cm. below the tip of the ensiform cartilage. The flattened hand could be passed over the right anterior superior iliac spine, and under the right costal margin a resistant rounded mass (the uterus) could be felt. Deeply pressing-in a stethoscope at this point the fœtal heart could be plainly heard. When the patient was standing, the buttocks appeared small and thrown together, the hips very narrow. When she was lying down, the thighs could not be extended beyond an angle of 35 degrees, nor abducted more than five degrees, save by flexion and internal rotation, and all movements were much limited.

Spine.—No lateral deviation. Both thoracic and lumbar spines presented a simple forward bend which brought the ensiform close to the symphysis, and the head several feet off the table, making a prone position impossible. The interspinous intervals were lost from the sixth dorsal to the fourth lumbar, but this latter interspace was plainly palpated, and was used for spinal anæsthesia.

Pelvic measurements:—

Interspinous	...	...	...	20·5 cm.
Intercristal ...	...	...	...	25·0 „
External conjugate	...	...	...	17·5 „
Bitrochanteric	...	...	...	22·0 „
Post-sagittal	...	...	...	4·0 „
Interischial	...	...	...	2·5 „

The finger could not be passed into the vagina in front of the ischial tuberosities.

The pregnancy was of about 5 months, and it was plainly impossible for her to carry to term, on account of lack of space in the abdomen, whilst it was equally impossible to deliver her through the vagina.

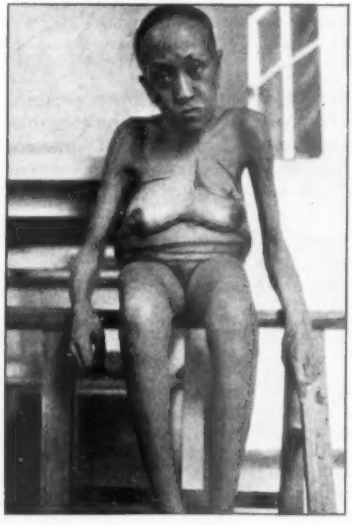


FIG. 1.

Dr. Wagner decided that it would be better to try to do a preliminary resection of ribs, and removed, on the right side, portions of the 7th, 8th, 9th, and 10th ribs with the costal cartilages and ensiform process. A small wound in the pleura was made and repaired, but the patient became cyanotic, and continued so for the next

five days. Unfortunately, four days after the first operation, she went into labour. An incision with local field-block was made parallel to the previous incision, and two inches below it. The uterus was incised through the fundus which could be brought into the incision. The uterine incision gaped widely and considerable difficulty was experienced in closing it. It was impossible to get at the lower uterine segment. The tubes were tied. In spite of transfusion, the patient became very cyanotic and died fourteen hours after operation.

A post-mortem examination showed marked pulmonary emphysema. There had been some extravasation of blood into the abdominal wall, apparently as a result of the first operation. Dr. Wagner considers that it would have been better to have tried to operate in one stage with heavy retraction of the ribs, but in any case there would have been considerable difficulty in getting any adequate exposure of the uterus.

The pelvis, which is shown in figures 2 to 5, is a most remarkable one, showing a healed osteomalacia with the typical deformities seen in a severe case of the disease.

These are the bony measurements of the specimen :—

Interspinous	19·5 cm.	
Intercristal	23·5 „	
True conjugate	8·0 „	approx.
Available conjugate	6·0 „	„
Oblique	9·5 „	
Interischial	2·25 „	
Between the outer edge of the acetabula ...	15·75 „	

Sacral index, 7·5 cm. by 8·5 cm. breadth.

The sacrum was firmly ossified to the ilia, and the transverse process of the last lumbar vertebra firmly joined by bone to the sacrum.

The lumbar vertebræ were ankylosed to each other by their transverse processes and spines, the ligaments having become ossified.

The second specimen is one from a woman who was admitted to the Peiping Union Medical College Hospital on July 3, 1933, having been in labour for three and a half days. She had active osteomalacia, and the deformity of the outlet was so severe that it was out of the question to deliver by that route. The child was dead, and pus was running from the uterus.

The details of this case are as follows :—

Mrs. L. C., aged 43, Hospital No. 40773, was admitted to the Peiping Union Medical College Hospital on July 3, 1933. She had been in labour for three and a half days. The membranes had ruptured on July 1, at 7 p.m., and she had been examined outside by an old-type midwife. The left leg had been swollen since labour began, and she was at term.

She had a history of pain in the back and legs, beginning when she was aged 38, i.e. three years after the birth of her last, and fifth, child. She had had typical osteomalacia symptoms. These became milder about the age of 40, but she was conscious of being shorter in height than before this illness. She had suffered from tetany from time to time during the disease. The abdomen was now distended, the bladder full, the fœtus dead, the os fully dilated, and there was purulent fluid exuding from the vagina, with the characteristic odour of gas bacillus infection. The left labium majus was much swollen.

The pelvic measurements were as follows :—

Interspinous	17·0 cm.
Intercristal	25·0 „
External conjugate	18·0 „
Interischial	4·5 „

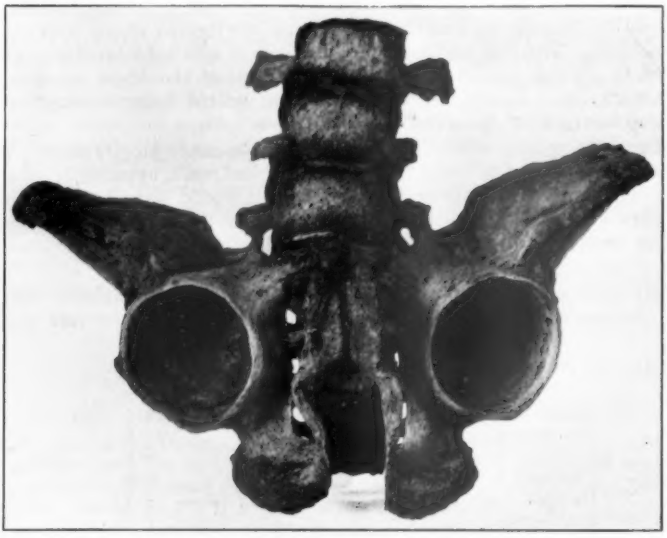


FIG. 2.—The Shansi pelvis: Front view.

FIG. 3.—Superior strait.

FIG. 4.—Inferior strait.

FIG. 5.—Side view.

It was manifestly impossible to deliver the fœtus per vaginam, and the uterus was in tetanic contraction.

The patient was anæsthetized with open ether at 8.30 p.m. on July 3, 1933, and a rapid Cæsarean hysterectomy was performed, the abdomen being drained by five cigarette drains. Gas bubbles were felt under the peritoneum of the broad ligaments and the back of the uterus. She went on fairly well till July 6, when she rapidly sank and died of acute septicæmia.

Her blood calcium on the early morning of July 4 was 7·32 mgm. per 100 c.c. of serum, and her blood phosphorus 3·16 mgm. per 100 c.c. of serum.

The X-ray examination showed deformity with fractures of the pelvis and osteoporosis.

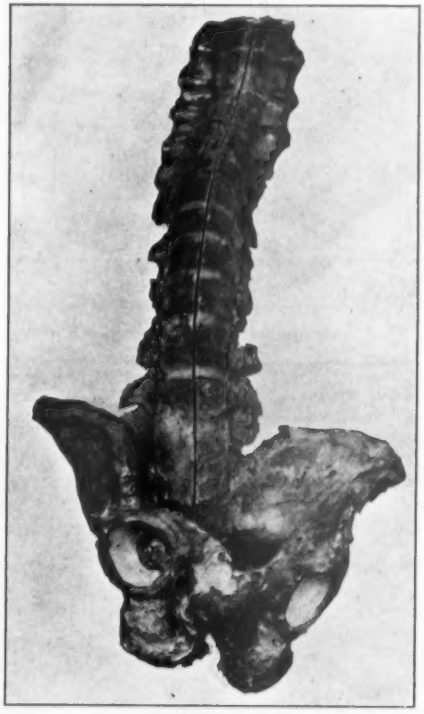


FIG. 6.—The Peiping pelvis and spine.

Dr. C. H. Hu made a very careful autopsy and secured the pelvis and spine (figs. 6, 7, and 8).

The following extracts are made from his autopsy report:—

Bones: In the middle of the following ribs, a degree of swelling, representing healed fractures, is noted on their inner surfaces. These ribs are the left 5th, 6th, 7th, 8th, 9th, and 10th, and the right 3rd, 4th, 5th. The pelvic bones are markedly deformed; the right half of the pelvis is pushed forward beyond the midline and the angle formed by the pubic bones becomes very narrow and admits only two fingers. Bone-marrow of femur moderately hyperplastic. The spinal column shows marked lumbar lordosis and left thoracic scoliosis. Longitudinal section of the vertebral column shows marked thickening of the central portions of the

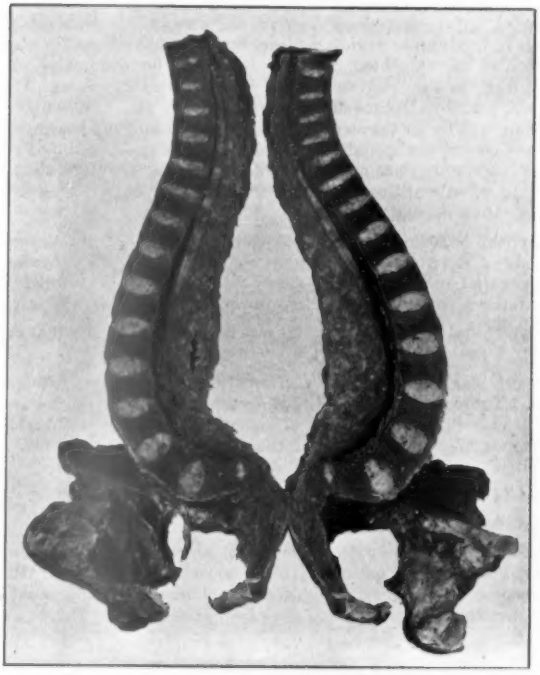


FIG. 7.—Antero-posterior Section.

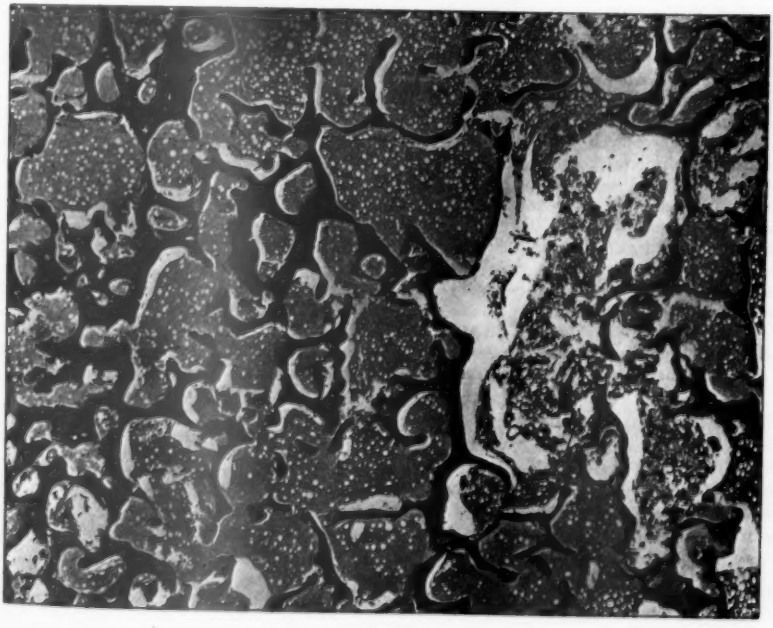


FIG. 8.—Microscopic Section of Vertebra.

intervertebral discs in the lumbar region with increased concavity of the superior and inferior surfaces of the bodies of vertebræ. Small irregular honeycombed cavities or spaces, measuring up to 5 mm. in diameter, are found in the cancellous bone of practically all the thoracic and lumbar vertebræ removed at autopsy (from 4th T. down). These spaces are present, one or two in each upper thoracic vertebra, situated midway between the intervertebral discs, on the concave side of the spinal column, close to the periosteum. In the lower thoracic and upper lumbar vertebræ they are present in large numbers, forming a zone extending anteroposteriorly across the middle of the vertebræ. In between these spaces the bone trabeculæ appear to be thinner than normal.

Microscopically, the bone-marrow of the femur showed moderate hyperplasia. The bone-marrow of the body of a lumbar vertebra was very cellular. The trabeculæ in the central portion were very thin; in many places they were absent. In addition a few irregular large spaces containing a small amount of homogeneous pink staining material were found.

The fœtus showed fœtal rickets (fig. 9). It was a male, weighing 3,000 grammes (Hospital No. 40777).

The X-ray report was as follows:—"*Extremities*: Evidence of osteoporosis at the ends of the long bones. There is irregularity of the epiphyseal ends of the radii, ulnæ, femora, tibiæ and fibulæ. This finding is typical of rickets, though not marked. *Ribs*: There is definite, though moderate, enlargement of the sternal ends of the ribs. Flaring of ribs noticed on both sides."

Dr. Hu's report of the autopsy contained the following notes:—

"The parathyroids could not be found.

Bones: Ribs. The costochondral junctions show slight enlargement, with slight broadening of the lines of ossification. Humerus, radius, ulna, femur, tibia and fibula are longitudinally cut open. Their lines of ossification show no visible change to the naked eye that is indicative of rickets."

But the microscopical examination proved quite definite:—

"*Ribs*: The line of ossification is very irregular, due to the presence of large or small islands of cartilaginous tissue remaining uncalcified in the marrow cavity. The cartilage cells above the line of ossification show a rather disorderly arrangement. The blood-vessels in the ossifying zone show marked congestion. The bony trabeculæ, even a long way from the line of ossification, still show numerous areas of osteoid tissue. The bone-marrow of the rib is not remarkable. *Humerus*: The lower end of the humerus also shows a very irregular line of ossification. Broad or narrow tongue-like protrusions of cartilage are present in large numbers in between areas of myeloid tissue which is rather acellular, somewhat œdematous, and markedly congested. *Femur*: The upper end of the femur shows only slight irregularity of the line of ossification, there being only a few small areas of cartilage remaining incompletely ossified. The lower end of the femur, on the other hand, shows much less complete ossification of the cartilaginous tissue. Occasionally a small patch of degenerating cartilaginous tissue containing shrunken cartilage cells, the nuclei of some of which take a pinkish stain, is present. *Tibia*: The upper end of the tibia shows very marked irregularity of the line of ossification. Many long or large tongue-like processes of cartilaginous tissue are left behind, remaining uncalcified. The myeloid tissue in between these cartilaginous masses is intensely congested, and oftentimes markedly hæmorrhagic. There is a good deal of œdema, but the number of myeloid cells is small. The lower end of the tibia also shows well-marked disturbance in ossification. The change is similar to that found in the upper end of the same bone. *Vertebra*: A horizontal section of the vertebra also shows slight irregularity of the line of ossification."

The spine of this mother with osteomalacia shows well the bulging of the intervertebral discs into the osteoporotic bodies. This is a characteristic feature of osteomalacia, and the characteristic spinal deformity is in part due to it. The condition has been well described by Beadle [2] in his monograph on "The Intervertebral Discs." The spaces in the vertebræ described by Dr. C. H. Hu in the autopsy report have been noted by Schmidt [26] as occurring in sections of a rib

from a case of osteomalacia, but as far as one knows they have not been described as being found in the vertebræ.

It will be noted that this paper is entitled: "Adult Rickets (Osteomalacia)." The time has come when it should be frankly recognized that these are one and the same disease.

FIG. 9.

It is now possible, as will be seen later on, to bring out more clearly than before the intimate connexion between adult rickets, fœtal rickets, infantile rickets and late rickets. Granted that the mere fact that an osteomalacic mother has a child with fœtal rickets does not prove the identity of the disease, the evidence of the intimate connexion of the two has become so full as to make it extremely unlikely that they have no causal connexion.

In fact the evidence is such as to make it very doubtful in some cases whether the disease should be classified under late rickets or osteomalacia, and it is clear that what one previously considered as classifying points between osteomalacia and rickets can no longer be maintained.

Take an example. The typical deformity of the pelvis in a case of rickets consists in the flattening of the pelvis, the outstanding alteration in the sacrum being an increase in the transverse convexity, whereas the typical deformity of the pelvis in a case of osteomalacia shows itself in the marked concavity which the sacrum acquires, and in the marked narrowing of the outlet, and in the formation of what is practically a triradiate pelvis. But Ogata [3] has pointed out that whereas in Europe the children are kept on their backs previous to walking, in Japan they sit in straw baskets or are carried on the back in a sitting posture, and in these cases you do not get the typical flat pelvis, but one which approximates to what one has called the osteomalacia type.

With regard to these deformities, Park [4] also writes as follows:—

"I wish to point out that the deformities caused by rickets follow different patterns at different age-periods, depending entirely on the time in the child's life when the rickets develops and flourishes. . . . Indeed, from the fifth year on, rickets bears an increasingly close resemblance to osteomalacia."

Further experience in the clinical signs and symptoms of the disease has revealed a very marked difference, which I have noted in previous papers [1, 24], in the severity with which the affection attacks various parts of the body. There is also a very great difference as to the amount of suffering experienced by various patients.

Here is a patient aged 29. Her disease commenced at the end of a prolonged lactation (four years) with the onset of another pregnancy. During this pregnancy the disease progressed rapidly, causing severe deformity of the chest, but not affecting the pelvis to any marked degree till after the spontaneous birth of the full-term child, when the pelvis began to be affected, and in less than two months was fractured and so deformed that a spontaneous labour would have been out of the question. And except in the last two months she seems to have suffered surprisingly little from pain.

The details of this case are as follows:—

Mrs. P. J., aged 29, Chinese, Hosp. No. 42452, married at the age of 23. She bore a full term, healthy baby when she was 24. Nursed the baby for four years. One month later impairment of appetite. January 1933, she had some respiratory difficulty. February 1933, deformity of chest and shortening of stature were noticed. April 1933, pain in legs and difficulty in walking. On September 6, 1933, a full-term child was born without assistance, and the patient was able to get up and walk in a month. Her milk was abundant but of poor quality, the calcium content being very low, 17·7 mgm. per 100 c.c., and the fat content deficient. Her blood calcium on admission was 7·3 mgm. per 100 c.c. of serum, and blood phosphorus 4·0 mgm. per 100 c.c. of serum. She was admitted on November 11, 1933. The baby was puny, the subject of rickets, almost certainly fœtal, and died twenty-four hours after admission. Measurements of mother's pelvis:—

Interspinous ...	...	...	23·5 cm.
Intercristal ...	...	...	25·5 „
External conjugate	...	...	15·5 „
Interischial ...	...	...	5·5 „

Marked kyphosis and scoliosis.

The pelvis shows deformity and fractures which have come on since September 6, 1933.

According to Schmorl [5], the chronological sequence of rickety manifestations is as follows:—

Costochondral articulations.

Lower epiphysis of femur.

Upper epiphysis of humerus, tibia and fibula.

Lower epiphyses of radius and ulna.

Upper epiphyses of femur, metatarsus and phalanges of feet.

But one sees no reason why the deformity in adults should fall on the chest before the pelvis. Ballin [6] points out that in hyperparathyroidism there is the same uncertainty as to the localization of the bony changes.

Looking at these facts about the genesis of rickety deformities of the pelvis one is led at once to the consideration of another form of deformity, i.e. that of the "funnel" pelvis. In one of my earlier papers [24] on osteomalacia, I hinted that it was possible that some, if not most, of these pelves were really due to mild forms of osteomalacia.

I would now propose to go further and reclassify the flat pelvis, the funnel pelvis, the osteomalacic pelvis and the pseudo-osteomalacic rickety pelvis in the following way:—

Deformities of the pelvis due to rickets:

(1) *Flat pelves* due to rickets in infancy, before walking has commenced and where the child has been kept on its back.

(2) *Triradiate pelves* due to rickets in infancy when, instead of lying down, the the child is carried about in a sitting posture.

(3) *Funnel pelves* due to rickets in childhood or adolescence.

(4) *Triradiate pelves* due to adult rickets, i.e. osteomalacia.

Of course a deformity due to rickets may also be grafted on any of the congenital forms of deformity of the pelvis, such as a small round pelvis, and the rickety deformity of the pelvis may be modified by the development of scoliosis or kyphosis.

It may be asked what evidence there is for so definitely classifying the funnel pelvis amongst those whose genesis is due to rickets, because the characteristic form of the pubic arch after infantile rickets is a very wide arch.

(1) During the last few months two foreign patients have come to me, neither of whom was aware that there was anything wrong with the pelvis. Both of them are marked examples of funnel pelvis, the interischial diameter being below 7 cm. in each case, and the posterior sagittal diameter being also somewhat diminished. In the one case there was a frank history of rickets in childhood, and the patient has a moderate amount of bow leg. In the other case the patient did not walk till she was sixteen months old, and then very unsteadily for another year. And her mother, who knew what rickets was, having suffered from it herself, was of the opinion that the surmise that her daughter had had rickets was correct.

In these cases, as a rule, the infantile rickets has not been very severe, and although in several other cases in the last ten years I have been able to elicit a history which pointed to rickets, as a rule the patients know little about their past history in this respect.

(2) Twice in patients who were developing osteomalacia, I have seen the interischial diameter diminish whilst under treatment, so that when cured they were left with what, were it not for the history, would be deemed a typical funnel pelvis.

(3) Here is another woman, a Chinese, whose three previous labours were normal, and who came for her fourth labour with a typical funnel pelvis, needing a

hard and difficult forceps extraction in which the child nearly died. She had a blood-calcium of 8·5 mgm. per 100 c.c. of serum, and it was clear that she had a mild osteomalacia.

In these cases there is little if any alteration in the measurements of the inlet, and from the point of treatment it is imperative that they should be diagnosed early; for the majority, if at all marked, need a delivery by Cæsarean section. Otherwise not only does one run the risk of having to end the labour by a perforation, but even where a child has been delivered through the vagina, the pelvic floor and possibly rectum are apt to be seriously damaged, leading to lifelong disability.

Another interesting clinical phenomenon in rickets is that of the development of Harrison's groove. This is "a furrow or concavity which runs horizontally across the lower plane of the thoracic wall at the level of the diaphragm and extends anteriorly from the base of the ensiform cartilage to the posterior folds of the axilla. Generally it is less marked on the right than on the left side due to the underlying support of the liver" (Hess).

It may be noted in mild cases of rickets, and is supposed to be due to the tugging of the diaphragm on a weakened chest well.

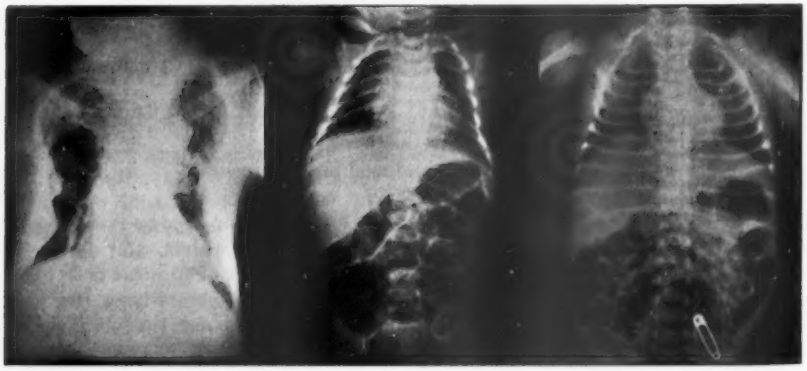


FIG. 10.—Harrison's groove in fœtal rickets and osteomalacia.

It is interesting to note the occurrence of this groove not only in infantile rickets, but both in fœtal rickets and in osteomalacia. Whether it develops before breathing commences is difficult to say, but as will be seen by fig. 10 it develops, not merely immediately after birth as in the case of antenatal rickets, but is also found in marked cases of osteomalacia. Its genesis is not perfectly clear and in our cases the groove appears to be a little high up on the chest.

Hess [7] has well shown the fallacy of the old reports on the question of the coexistence of osteomalacia and rickets. In the first place it is clear that many of the older reports on the non-coexistence of osteomalacia and rickets in regions where the former disease is common were inexact, due to the fact that the latter disease was not properly sought by skilled observers and that its milder symptoms were missed. Rickets was judged to be practically absent in North China, but the work of Ernest Tso [8] and the experience of the Pediatric Department of the Peiping Union Medical College Hospital has shown that so far from this being the case, it is very common in this locality.

We have also Green-Armytage's dictum [9] as regards the connexion between osteomalacia and rickets in India. He says: "Moreover, all babies born of osteomalacia mothers later tend to develop rickets. We have seen a great number of these children with typical rachitic phenomena between the years of one and eight." Finally, Ogata [3] in his second report on osteomalacia in the district of Toyama, Japan, gives figures to show that rickets was found plentifully in children in this region.

And in considering this question one has to remember the nature of the environment in the regions where osteomalacia is present in the Far East. The sun's rays are not filtered by the smoke of large cities, the amount of clothing worn by infants and young children varies immensely from practically nothing to full clothing, and an outdoor life is the usual thing for those who survive the heavy neonatal mortality which eliminates a large number of those most likely to develop rickets.

And when one comes to the question of late rickets and its relation to osteomalacia, our knowledge on this point has been materially advanced by the work of Stapleton [10] and of Wilson and her associates [11] in India. They have shown most conclusively that the two diseases blend into one another.

That the same is true, as regards China, is well shown by the following three cases:—

Miss W. H. H., aged 16, Hosp. No. 37244, was seen on July 15, 1933, in the Peiping Union Medical College Hospital.

She had been limping for four to six months. Coming from a poor family, at the age of 12 she became a maidservant. Her food had been mainly rice and vegetable. At about that age she had noticed a slight disability in walking, but it had not really troubled her till four months previously. Two months previously she had noticed that the left leg was adducted in walking. She has had little pain, but when present it was dull in character and in the bones. Menstruation had been present for three months. Her legs were bowed outwards to right, the right exhibiting a condition of bow leg, the left exhibiting a condition of knock the knee. On admission her blood calcium was 10·3 and phosphorus 3·1. Her interischial diameter measured 6·75 cm.

The report on the roentgenograms contained the following paragraphs:—

Legs: There is a mild anterior bowing of the right femur and mild bowing of the distal third of the right tibia. Periosteal new bone is seen along the medial aspect of the distal third of the right femur. The right leg shows marked deviation with the right ankle pointing toward the left foot; this deformity is more of an angulation of the leg at about the knee-joint, apparently due to maldevelopment of the proximal epiphysis and metaphysis of the right tibia. The metaphyses of the bones of both legs show localized absorption, slight expansion and irregularity. Along the shaft of the fibula at the junction of the middle and distal thirds there is some localized periosteal thickening.

Wrists: There is mild, but definite, generalized osteoporosis of the bones of the wrists and hands. The metacarpals appear shortened. The spectacular changes are in the metaphyses of the ulna and radius in both wrists—localized absorption, slight expansion and irregular outline, characteristics of adolescent rickets.

Pelvis: Generalized osteoporosis of the bones of the pelvis and both femurs. The trabeculæ of the bones are very coarse. There is marked, localized decalcification of the pubis and to certain extent the ischia. Mild but definite approximation of the acetabula is noted as in cases of mild osteomalacia.

The impression was that the findings in the metaphyses suggested adolescent rickets whilst the deformity of the pelvis suggested osteomalacia (*see* figs. 11 and 12, p. 14).

The second case is that of Miss C. C., aged 18, Hosp. No. 38581, admitted to the Peiping Union Medical College Hospital on December 20, 1932.

About March 1931, patient found herself getting weak, and she was seized by attacks of sharp pain, intermittent and radiating, starting from the middle of the left inguinal region and passing down the left leg. Two months later pain started in the left knee. In July

1931, the right inguinal region began to give pain, and shortly after the right knee also started. Since July 1932, she has been limping and found it difficult to assume the erect posture.

Her diet has consisted of two meals a day, flour, rice, and vegetable, no meat, eggs or fish.

Her pelvis showed contraction of the interischial diameter, slight rostration and she had typical pain and spasm of the adductors of the thigh.

Her blood calcium was 8·4 mgm. per 100 c.c. of serum and blood phosphorus 2·9 mgm. per 100 c.c. of serum. Chovstek's sign positive.

There was a distinct tendency to pigeon chest, and the costochondral junctions were somewhat enlarged. There was a definite knock knee (see figs. 13 and 14).

The X-ray report may be summarized as follows: All the bones seen are osteoporotic and slightly washed out in appearance. The pelvis is about normal in shape with slight narrowing of the pelvic arch. An old fracture is noted about two inches below the head of the right fibula. The epiphyseal lines of the lower ends of both femora are clouded which is suggestive of remnants of old rickets. Slight medial angulation noted at both knee regions.

All the visualized vertebral bodies appeared osteoporotic. The skull was normal in shape but the cranial bones presented a washed-out appearance.

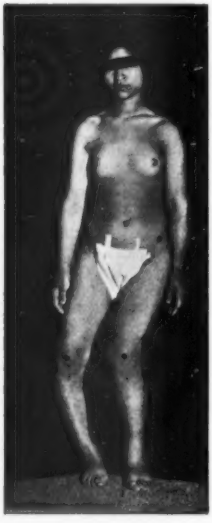


FIG. 11.

FIG. 12.

Late rickets (Case 1).

There is no doubt that in this case the pelvis illustrates the commencing deformity of an osteomalacia case, whilst the knock knee, and the epiphyseal lines of the radii and ulnæ, show the lesions one has been accustomed to associate with rickets.

The third case is the most remarkable of the three, for in it we see a complete sequence of late rickets, osteomalacia, and fœtal rickets.

Mrs. C. U. C., aged 30, Chinese, Hosp. No. 43815, was admitted to the Peiping Union Medical College Hospital as an emergency case in February 1934. She was in the thirty-eighth week of her first pregnancy; the membranes ruptured seven hours before admission,

labour having lasted about nine hours. Delivery of a living child from below was impossible, and the fœtus, though alive, was in distress, and died just as the Cæsarean section was starting. Her history was as follows: Menstruation started at the age of fourteen, and about three months later she began to suffer from pain in the thighs and later on in the back. It was worse on walking, and especially on going up hill. This went on, better in the summer, and worse in the winter, till she was married at the age of twenty. After marriage the pain became somewhat worse, and at the age of twenty-three, while helping to carry a box, she had spontaneous fractures of the left clavicle and left forearm. Since pregnancy started she has been much worse. In the fourth month she had diarrhœa, and during the last six months she has had much pain and disability, walking being practically impossible during the last three months. Since the beginning of pregnancy she has been off her food, and this has been marked during the latter half of pregnancy.

FIG. 13.

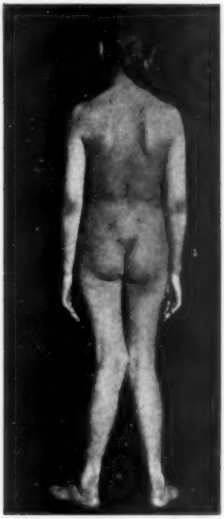


FIG. 14.

Late rickets (Case 2).

The diet during her girlhood was fair, but she was very little out of the house. After marriage the food was worse, and of late she has taken two meals a day of wheat-flour cakes, fried in sesame oil, rice gruel, maize cakes and a little celery cabbage.

Calculating the diet it works out as follows:—

Calories	1,146	
Protein	32·4	grm.
Fat	13·3	,,
Carbohydrates	223·6	,,
Calcium	0·06	,,
Phosphorus	0·276	,,
Vitamins	Poor	

Her blood calcium was 7·8 mgm., and her blood phosphorus 2·36 mgm. per 100 c.c. of serum.

She is short in stature with marked bow legs (fig. 15). The pelvis is deformed in the usual way (fig. 16), and the left clavicle and forearm show signs of old fractures (fig. 17).

The fœtus was a typical example of severe fœtal rickets, and its cord blood contained 8·83 mgm. of calcium per 100 c.c. of serum. The X-ray report on the fœtus was as follows:—

There is saw-like irregularity and fraying of the metaphyses of all the long bones of the extremities. The cortex of the bones is slightly thinned and osteoporotic. The sternal ends of the ribs show slight expansion. No periosteal changes seen (*see* figs. 18 and 19).

It may be justly said that this is a calcium rickets series. There is probably a phosphorus osteomalacia, but it is the rarer form, whilst in the West the usual form of rickets is the phosphorus deficiency one.

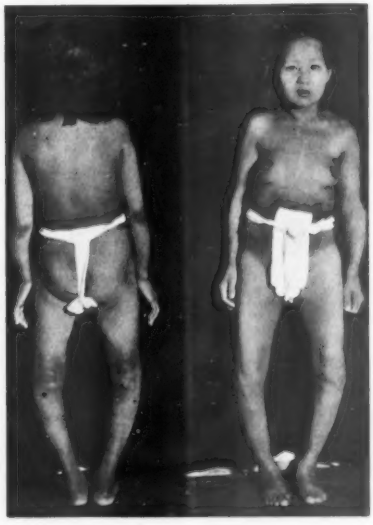


FIG. 15.—Late rickets (Case 3).

As Shipley, Park, McCollum and Simonds say [12] :—

"It must be remembered that rickets can be produced in the absence of vitamin D either by diminishing the phosphorus in the diet and supplying an optimum or excess of calcium, or by reducing the calcium and maintaining the phosphorus at or near optional concentration."

But it is a question whether the cause of rickets is merely a matter of absence of vitamin D and disturbance of the mineral balance.

The matter of the supply of calcium and phosphorus in the diet has been already mentioned and will be further discussed.

Dr. R. R. Hannon has pointed out to the writer that the question of the relation of the endocrine secretions to the causation and healing of rickets has still to be worked out. It is certain, for instance, that thyroid gland secretion plays its part in the matter, but whether by a direct action or by its influence in metabolic processes is not known. Rickets, like changes in the bone which will not be cured by cod-liver oil, may be associated with hypothyroidism, and it is possible that the secretion

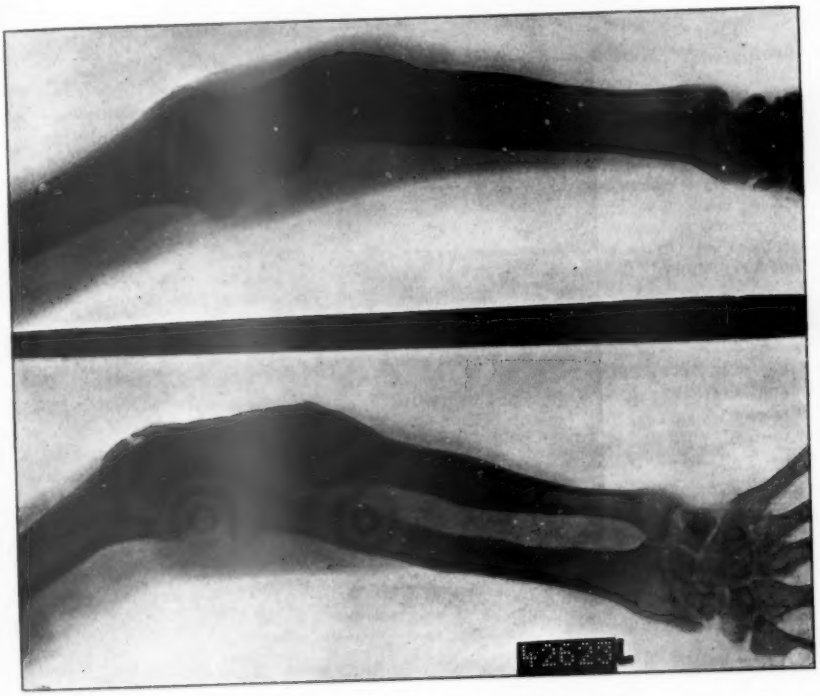


FIG. 17 (Case 3).

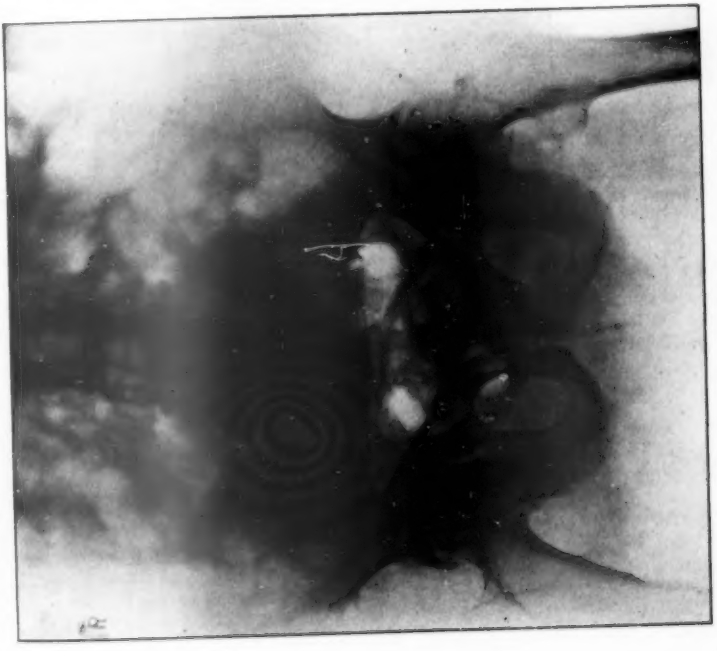


FIG. 16 (Case 3).

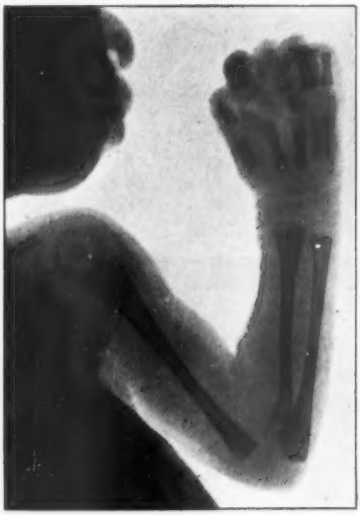


FIG. 18.

FIG. 19.

FIGS. 18 and 19.—Fœtal rickets (Case 3).

of the pituitary, adrenals and the parathyroids is not without its influence in the matter.

It must also be noted that tetany in babies born of osteomalacic mothers is by no means unknown.

Hess [7] says:—

"It has long been recognized that there is an intimate relationship between infantile tetany and infantile rickets. Indeed Kassovitz regarded tetany merely as a nervous manifestation of rickets, and Shipley, Park, and their colleagues refer to it as the low-calcium form of this disorder. Although tetany may occur occasionally in an infant free from rickets, from a clinical point of view it may be considered that practically all infants with signs of tetany, if followed long enough, are apt to develop rickets to some degree."

The question of the apparent absence of pain in the ordinary case of rickets has never yet been solved. But one has to remember that the majority of the cases of rickets in the West are apparently due to a phosphorus, rather than a calcium, deficiency. One also has to remember that the sensitiveness of an infant to pain is distinctly less than that of an older child or adult. Park and Eliot [13] note the occurrence of pain in the older child, and the occurrence of greenstick fractures, very similar to those one gets in osteomalacia.

Has any further evidence come forward which would modify our views as to the question of these diseases being due to a deficient diet, and in what respect does this deficient diet fail? In an article entitled "Osteomalacia and diet" [14] this question has been fully discussed. Here is a specimen diet which is representative of the food which Northern Chinese poor patients consume:—

Total calories	1,188
Protein	29·3 grm.
Fat	22·01 „
Carbohydrate	212·55 „
Calcium	0·249 „
Phosphorus	0·522 „
Vitamins	poor

This diet consists of varying quantities of corn bread, white flour, rice, millet, kaoliang and vegetables, with practically no meat, milk, eggs, or animal fats; sesame oil being mainly used for cooking.

Not only is the general caloric intake low, but the protein is of poor quality, the staple food is cereal, which is rachitogenic; the carbohydrate supplies 72·9% of the calories, the mineral supply is below the normal, and the supply of vitamins, especially vitamin D, is poor.

And in many of our osteomalacia cases the caloric intake is well below the figures given in this representative diet.

Compare this diet I have just given with that which Hamill's Report [15] lays down as containing the necessary requirements of a healthy working woman.

Total calories	2,500
Protein	90 grm.
Fat	75 grm. average (minimum 20 grm.)
Calcium	0·6 grm. minimum
Phosphorus	1·2 grm.

Carbohydrates may provide 50-70% of the calories, but if the percentage of calories derived from carbohydrates rises much above 66% the diet may be considered to be in need of improvement. Moreover, the protein should be first-class, and there is no first-class protein in the diet of these patients.

One of the interesting points about adult rickets (osteomalacia) is the early symptoms of the disease especially in pregnancy cases. It was pointed out in a previous communication [16] that excessive motion on the part of the fœtus was an early sign, and that under appropriate treatment with calcium and vitamin D these excessive movements would cease. Another of the early symptoms of a calcium vitamin shortage is pain in the back.

It is possible also that some patients who suffer badly from cramps in the legs towards the end of pregnancy are in a like condition, for occasionally a little irradiated ergosterol will entirely relieve this symptom. It may be argued that it does not follow that the medicine was the cause of the improvement, but it is certainly worth bearing in mind, for some of these so-called minor troubles give one's pregnant patients great discomfort.

To turn now to the question of fœtal rickets. Here are tables (Table I) showing the details of the first sixteen cases of the disease which have been diagnosed by us, and notes on three other cases (in Table II) which come very near to falling into the same classification. I think it is clear that, if sought, fœtal rickets will be found to be far from uncommon. It is certain that a very large number of pregnant women are living on the edge of a serious deficiency of vitamins and salts, as we have already demonstrated.

What are we to accept as the standard figures for calcium and phosphorus in the maternal blood stream and in the cord blood?

There is considerable variation in the figures given by Bogert and Plass [17, 18] and by Denis and King [19]. Peters and Van Slyke [20] place the average value between 9 mgm.-11·5 mgm. calcium per 100 c.c. of serum for normal individuals. Some workers, such as Bogert and Plass, give the figure for calcium at "term" at 9·1 mgm.; others such as Denis and King place it at 10-11 mgm. per 100 c.c. of serum. So that we shall not be far wrong if we average these latter figures and arrive at the following standard (mgm. per 100 c.c. of serum):—

Normal non-pregnant women:		
Calcium		10·25
Phosphorus		3·00
Pregnant women at term:		
Calcium		9·50
Phosphorus		3·10
Cord blood:		
Calcium		10·90
Phosphorus		4·50

Serum-calcium is supposed to be appreciably lowered in the later months of gestation in the mother and definitely raised in the newborn, though whether this is strictly physiological is not fully known. And so far there has been no adequate explanation given of the mechanism by which this concentration in the cord blood is carried out. The substances thus concentrated are those specially needed for the building up of new tissue in the fœtus. On the other hand, total plasma and serum proteins are lower in the pregnant and parturient woman than in the non-pregnant, and still lower in the fœtus at birth.

We have conducted extended investigations into the matter of the calcium and phosphorus figures in the blood-serum in our patients to see how far they correspond with the normal figures given above.

The calculations of the calcium have been made by Kramer and Tisdall's [21] method, and the calculations of the phosphorus by the Briggs' modification of the Bell-Doisy method [22]. Practically all have been done by one technician,

TABLE I.—FŒTAL RICKETS

TABLE I.—FŒTAL RICKETS

Date and number	Age Mother	Ca Mother	P Mother	Para	Mother's condition	Week of delivery	Method	Evidence of Rickets	Cord Ca	Cord P	After-history of child.
(1) Dec. 1927	32	—	—	V	Osteomalacia. Pulm. tb. Died 2 months later.	Term	C. S.	X-ray and Sections	—	—	Weight 2,040 grm. Died 5th day, hæmorrhage
(2) *23871* April 1929	38	4·7 mgm.	1·8 mgm.	VII	Osteomalacia. Tetany.	Term	Normal labour	X-ray	4 days 10·16 mgm.	pp. 8·25 mgm.	Rickets healed 38 days. Well.
(3) *34053* Nov. 1931	34	4·5 mgm.	3·1 mgm.	II	Osteomalacia. Pulm. tb. Died 3rd day.	38th	C. S. Hysterectomy	X-ray	7·6 mgm.	—	Improved slowly.
(4) *30741* Jan. 1931	38	7·83 mgm.	—	VI	Osteomalacia. Pulm. and spinal tb. Died 14th day.	Term	C. S.	X-ray. Clinical evidence. Sections.	10·6 mgm.	—	Died 65 hours after birth. Hæmorrhage.
(5) *34611* Jan. 1932	26	—	—	V	Early osteomalacia. No pelvic deformity.	38th	Normal labour	X-ray	8·8 mgm.	—	Rickets improved slowly. Well.
(6) *35880* May 1932	19	5·4 mgm.	2·9 mgm.	I	Tetany on verge of osteomalacia.	Term	Normal labour	X-ray	8·1 mgm.	4·2 mgm.	Rickets improved slowly Jan. 1934, Teeth characteristic.
(7) Jan. 1933	31	—	—	III	Osteomalacia.	Term	C. S.	X-ray	—	—	Baby doing well.
(8) *38841* Jan. 1933	24	4·65 mgm.	3·15 mgm.	III	Osteomalacia.	38th	C. S.	X-ray. Sections.	5·6 mgm.	—	Died in utero just before birth.
(9) *36682* July 1932	39	7·8 mgm.	2·0 mgm.	II	Osteomalacia. Late rickets.	Term	C. S.	X-ray	9·3 mgm.	4·4 mgm.	—
(10) *37465* Sept. 1932	25	8·3 mgm.	2·2 mgm.	I	Osteomalacia. Funnel pelvis.	Term	Craniotomy	Sections	—	—	—

TABLE I.—FŒTAL RICKETS (*continued*)

Date and Age	Age Mother	Ca Mother	P Mother	Para	Mother's condition	Week of delivery	Method	Evidence of Rickets	Cord Ca	Cord P	After-history of child
(11) *39549* March 1933	33	9·1 mgm.	2·7 mgm.	IX	Osteomalacia.	37th	C. S.	X-ray	9·1 mgm.	3·3 mgm.	Unknown.
(12) *40777* July 1933	43	—	—	V	Osteomalacia. *B. welchii* infection.	Term	C. S. Hysterectomy	X-ray. Sections.	—	—	—
(13) *43773* Feb. 1934	27	8·35 mgm.	1·33 mgm.	IV	Osteomalacia.	36th	C. S.	X-ray. Clinical evidence.	10·8 mgm.	2·66 mgm.	Well.
(14) *43746* Feb. 1934	30	9·15 mgm.	2·0 mgm.	IV	Osteomalacia.	38th	C. S.	X-ray. Clinical evidence.	9·35 mgm.	—	Well.
(15) *43817* Feb. 1934	30	7·8 mgm.	2·36 mgm.	I	Osteomalacia. Late rickets.	38th	C. S.	X-ray. Sections.	8·83 mgm.	—	Stillborn.
(16) *43804* Feb. 1934	32	8·4 mgm.	3·16 mgm.	VII	Avitaminosis. Pt. apathetic; 5 children died of convulsions in childhood.	Term	Normal labour	Clinical evidence confirmed by X-ray	—	—	Well.

TABLE II.—FŒTAL RICKETS

The following cases are appended because their symptoms point so strongly to the presence of a pre-rickety fœtal condition, and it is noteworthy that all three are the low calcium type of rickets in contradistinction to the usual infantile type which is a low phosphorus rickets.

(1) *31260* March 21, 1931	50 days old	Tetany commenced on the 45th day	Rickets suspected on admission	Confirmed by roentgenographic evidence	Ca 7·8 mgm. on admission.
(2) *36217* June 6, 1932	Born in Hospital	Tetany commenced on the 21st day (Mother, on July 7th, 1932, Ca 8·5, P 4·1.	Rickets suspected	Confirmed by roentgenographic evidence Milk was calcium short.)	Ca 7·8, P 8·8 on readmission.
(3) *36291* June 13, 1932	77 days old	Tetany commenced on the 28th day	On admission marked rickets	Roentgenographic evidence of rickets	Ca 7·5, P 6·5 on admission.

Mr. Chuan, whose figures have been checked up from time to time by some of my staff, especially by Dr. S. W. Lee.

There has been no selection of patients except as noted below.

Obstetric cases: Chinese pregnant women, general average :—

(1,448 patients, calcium and phosphorus)
(110 patients, calcium only)

Calcium	9·43
Phosphorus	3·30

Omitting the above 110 cases, which were more or less a selected group, we have the following figures :—

Chinese pregnant women, 10th to 20th week. 20% of the cases :—

Calcium	9·70
Phosphorus	3·48

20th to 30th week. 24% of the cases :—

Calcium	9·64
Phosphorus	3·20

30th week to term. 56% of the cases :—

Calcium	9·64
Phosphorus	3·26

Foreign pregnant women (66 patients) :—

Calcium	9·67
Phosphorus	3·28

Gynæcological cases: Chinese gynæcological patients (408 patients) :—

Calcium	9·62
Phosphorus	3·40

Foreign gynæcological patients (36 patients) :—

Calcium, average	10·13
Phosphorus, average	3·51

It will be noted that the whole of the figures run fairly parallel with the standard figures for the pregnant and non-pregnant women. But when one comes to deal with these cases more closely, it is found that 260 Chinese pregnant patients, or 16·68% of the total, had a blood calcium between 8·51 and 9·00. 85 Chinese patients, or 5·45%, had a blood calcium between 8·01 and 8·51, and in 38 Chinese patients, or 2·44%, the blood calcium was below 8 mgm. per 100 c.c. of serum.

Scrutinizing these last 38 cases, one finds that they classify themselves into :—

Cause unknown	7
Pregnancy and osteomalacia	7
„ „ accidental hæmorrhage	2
„ „ placenta prævia	3
„ „ eclampsia	2
„ „ cardiorenal disease	2
„ „ intestinal trouble (typhoid and dysentery complicating pregnancy)	2
„ „ pyelonephritis	2
„ „ anæmia	5
„ „ sepsis	2
„ „ tuberculosis	4

Turning to the cord blood figures, these are as follows:—
Chinese newborn infants (200):—

Calcium	... 10·71
Phosphorus	... 5·21

Foreign newborn infants (30):—

Calcium	... 10·9
Phosphorus	... 5·34

And again the figures bear a close resemblance to those obtained by other authors.

There is another interesting question. Is it possible that some of these infants have got a condition bordering on rickets, the signs of which might be visible in sections of the bones before one could obtain evidence by means of a roentgenogram? To try to settle this point a number of sections have been compared.

What does one understand as being the normal for such a section? Here is Turnbull's [23] summary of the position:—

"In a normal bone from a fœtus two main zones can be recognized in the cartilaginous epiphysis; an upper zone of resting cartilage and a lower zone of proliferating cartilage. The zone of proliferation itself shows three zones from above down: (1) A zone in which the multiplied cartilage-cells are arranged in groups which above are very small and round, but inferiorly increase in size and length; (2) a zone in which they are grouped in short, oval, vertical columns; and (3) a zone in which they are greatly swollen, and are arranged in long, wide columns. Zones (1) and (2) merge into each other, and are usually taken together as the zone of columns; zone (3) is the hypertrophic zone. The hypertrophic zone lies immediately above the epiphyseal line. The epiphyseal line is even and straight, except for one or more shallow upward indentations where relatively large vessels from the diaphysis anastomose with vertical chondral vessels. All the hypertrophic zone except a shallow strip in its upper part, is calcified, and constitutes the zone of provisional calcification."

The sections of the bones of fœtuses examined fall into three categories.

(*a*) Osteoporosis without any sign of fœtal rickets. A very good illustration of this was published in the paper by Maxwell and Miles on "Osteomalacia in China" [24]. The various zones spoken of above are all present, the epiphyseal line is even and straight, but the bone is markedly deficient in osseous tissue when compared with a normal specimen. The roentgenogram shows no sign of rickets. It is possible that in this case treatment of the mother before labour had modified the microscopical appearances.

(*b*) Fœtal rickets without any question. Both in sections and in the roentgenogram one has ample evidence of the affection.

(*c*) Early fœtal rickets, the roentgenogram showing no signs of the affection, but sections revealing a commencement of the disease. Here is an example of this class, there being probably many more existent, but undetected, as if the child lives and is properly fed healing takes place speedily. If not properly fed, the child will probably develop, early on, the signs of rickets.

Baby C. T. K., Hosp. No. 37465, was born dead on September 28, 1932. It had to be delivered by embryotomy.

The mother had osteomalacia. Her blood calcium and phosphorus figures were as follows:—

Calcium 8·3 mgm. per 100 c.c. of serum. Product 18·26.
Phosphorus 2·2 mgm. per 100 c.c. of serum.
On account of these a roentgenogram was taken of some of the baby's bones.

The report by Dr. T. S. Jung, of the X-ray Department, runs as follows:—

"On the whole the diaphyseal ends of the femur appear quite smooth and rounded. Slight tendency to floring is seen at one end of the humerus. Findings are not conclusive for fœtal rickets." But Dr. Ngai's report (Pathological Department) on these bones runs as follows:—

"The osteochondral junctions of these long bones show very slight irregularity in the line of ossification, especially the lower end of the femur and the upper end of the humerus. The costochondral junctions of the ribs are slightly enlarged, suggestive of a rosary, and show hazy and irregular lines of ossification. Microscopically: *Ribs*. The cartilaginous portion is not striking. The costochondral junction shows a moderate swelling. The line of ossification is irregular instead of being smooth and even as in the normal cases. Portions of the cartilage protrude into the narrow cavity for a considerable distance. In these cartilage protrusions blood capillaries are moderately abundant and are distended by red blood cells and calcification is not seen. In this zone, especially in the region near the cortex, the marrow cavities are slightly fibrotic, and contain few hæmatogenous cellular elements. The rest of the marrow cavities is normal except some post-mortem necrosis of the blood cells. The bony cortex and the trabeculæ also contain many foci of bluish cartilaginous masses, even for a considerable distance away from the metaphysis (*cf.* fig. 20, p. 26). *Humerus*: The upper end shows a slightly irregular line of ossification where a few cartilage tongues protrude toward the diaphysis. In these cartilage tongues the blood capillaries are much distended by red blood cells. The marrow cavities are not striking. *Femur*: The lower end shows the same type of change as above described, but the process is slightly more marked. In the epiphyseal cartilage portion, the small centre of ossification shows slight tendency to bone formation and calcification. The cartilaginous trabeculæ, which are in few places covered by thin layer of bone, project into the centre and often anastomose with one another."

So that I think it is justifiable to say that there are probably many cases of infants in whom, given an unfavourable environment, and improper food, rickets will develop very early.

On the other hand, judging from the fœtuses falling into the first category, is it not possible that there are a certain number of cases in which the deficiency is not one of avitaminosis, but of calcium starvation?

By the time the affection has advanced to the stage at which there is roentgenographic proof of rickets, it has become sufficiently stubborn to need considerable treatment—at least six weeks to two months—before the lesions can be seen to be healed.

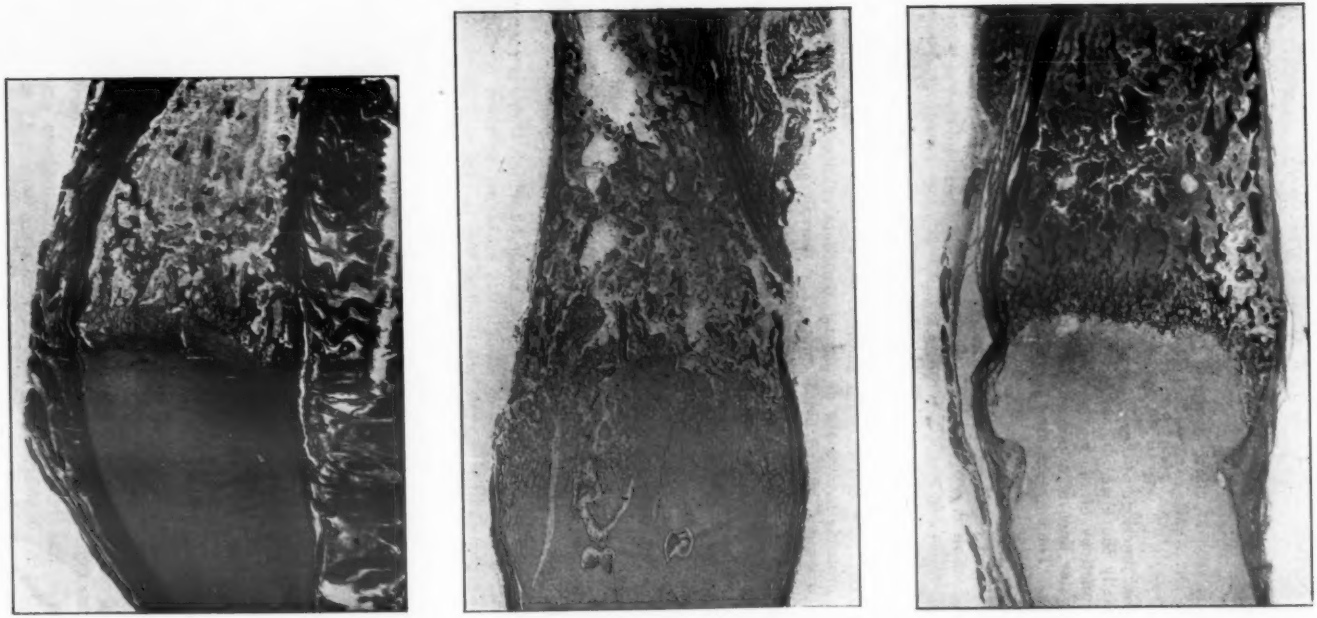
Another point is raised by these tables. Is it possible to predict fœtal rickets before birth? Are the calcium and phosphorus figures of the mother's blood sufficient to suggest this possibility? Here are figures taken from the patients cited in Table I:—

FŒTAL RICKETS

Case II.	Mother's	Ca 4·7, P 1·8.	Product 8·46
„ III.	„	Ca 4·5, P 3·1.	„ 13·95
„ VI.	„	Ca 5·4, P 2·9.	„ 15·66
„ VIII.	„	Ca 4·65, P 3·15.	„ 14·64
„ IX.	„	Ca 7·8, P 2·0.	„ 15·60
„ X.	„	Ca 8·3, P 2·2.	„ 18·26
„ XI.	„	Ca 8·35, P 1·33.	„ 11·10
„ XII.	„	Ca 9·15, P 2·00.	„ 18·30

It will be seen that in every case the product is under 20, and in the majority very much under this figure. But what of these figures? Are they really significant?

Whilst this table was being made out another osteomalacia case (Case XI) came in with obstructed labour. The mother's calcium was 8·35 mgm., and her phosphorus 1·33 mgm. per 100 c.c. of serum, making a product of 11·10. The



(*a*) (*b*) (*c*)

FIG. 20.—Osteochondral junction in (*a*) normal infant; (*b*) a case of very early fœtal rickets; (*c*) a case of marked fœtal rickets.

child's cord blood gave a calcium of 10·8 mgm., and a phosphorus of 2·66 mgm., or a product of 28·72. On these findings a diagnosis of fœtal rickets in the newborn was made and confirmed by roentgenograms.

Park in a paper on "Some Aspects of Rickets" [4] writes as follows:—

"Rickets is present or absent according to the relationship which prevails between the rate of lime-salt deposition and the rate of bone growth. If the latter just corresponds to the former, complete calcification prevails. If the latter exceeds the former, rickets develops."

If one expands the idea of bone growth to include bone replacement which goes on all through life, the dictum is also true of osteomalacia.

The practical result is that in his formula $\frac{Ca \times P}{\text{rate of bone growth}} = K_2$, if the rate of bone growth increases, the Ca × P must also increase for metabolism to be maintained at a constant figure.

It is possible that it would be a truer representation to translate the terms "bone growth" in the adult into "bone metabolism." It would explain the osteoporosis which one sometimes gets with hyperthyroidism, in terms of an attempt of the body to maintain the Ca × P figure to correspond with an increased metabolism. It would also explain the unwillingness of an osteomalacia patient to increase metabolism by movement as a desire on the part of the body to try to depress metabolic change to correspond with the calcium starvation.

What is the normal calcium figure in the serum in the adult? Park puts it as a more or less constant value of 10 ± 1 mgm. per 100 c.c. of serum, or a product (Ca × P) varying roughly between 20 to 37, but in any case not below 20.

In the very young the phosphorus figure is $5 \pm 0{\cdot}5$, and a factor of 50 may exist with evidence of rickets in premature and very young children.

So that one has to remember that Howland and Kramer's figure of 30 has to be accepted with caution in the very young. Below a figure of 30 you are certain to have rickets, but a figure over 40 does not, taken by itself, preclude its possibility.

Thus "the ætiology of rickets has two sides, so to speak, and some factors operate by affecting calcification and others by influencing growth."

I am inclined, however, to disagree with Park when he states: "If the patient is an adult, the calcium × phosphorus product under 30 does not have special significance."

Take for instance the following case:—

Mrs. C. L., aged 22, admitted to the Peiping Union Medical College Hospital on October 13, 1932, in great pain, bedridden, and four months pregnant.

Typical osteomalacia pelvis. Interischial diameter 6 cm.

	Ca and P	Product	Date
Bedridden and unwilling to move for the pain ...	Ca 8·8		
	P 1·6	14·08	Oct. 14
Pain improved, but still unwilling to move, walking round bed	Ca 8·5		
	P 2·5	21·25	Nov. 17
Still pain in chest and thighs but beginning to move about	Ca 9·0		
	P 2·3	20·70	Dec. 21
Walking about a little	Ca 8·6		
	P 3·4	29·24	Jan. 16
Walking well, pain all gone	Ca 8·8		
	P 3·8	33·44	Feb. 13
Condition good	Ca 9·0		
	P 4·2	37·80	Mar. 9

Cæsarean section on March 15, 1933.

Treatment throughout: Irradiated ergosterol, cod-liver oil, ultraviolet light and massage, calcium lactate 0·6 grm. daily.

As to the question of the possible prediction of fœtal rickets, it is certainly to be looked for in cases where the product of calcium and phosphorus in the mother's blood is below 20, and especially if the calcium factor is distinctly low. Where the calcium factor is high and the phosphorus figure low the probability is not so great.

Another question is raised by these findings: How far can one push back in antenatal life the roentgenographical appearances of rickets? It is not always easy to be actually sure of one's dates, but there was no doubt about the accuracy of the data in the ninth case in our list of cases of fœtal rickets (*see* Table I). In this case the baby was delivered by Cæsarean section shortly after the bursting of the waters. It was at least twenty-one days from term and the roentgenographic evidence of rickets was unequivocal. We have not yet definitely demonstrated fœtal rickets *in utero*, but in view of this evidence there is no doubt that there is a possibility of so doing, given a case with the fœtus lying so that a good view of the ends of the long bones could be obtained.

That there is little doubt about the genesis of these cases is proved by the history of two of our patients, whose children presented the signs of fœtal rickets, but in whom the avitaminosis and calcium starvation were arrested before they acquired the pelvic deformities of osteomalacia, so that there was no difficulty from the obstetrical standpoint in their having more children by the normal route.

Both these patients were treated, and were given instruction as to diet and the necessity of sunlight and movement, and both have subsequently borne children without any sign of fœtal rickets, though in the second case it is doubtful whether the child was not a weakling.

Here are the details of these two patients:—

Case I.—Mrs. C. C. S., aged 19, a primipara, was admitted to the Peiping Union Medical College Hospital on May 4, 1932, in labour.

She had been well till the seventh month, and then was ill in bed for six weeks without fever. She did not want to eat, and at the best she was getting a very deficient diet which worked out as follows:—

Total calories	963·0	
Protein	33·1	grm.
Fat	17·9	„
Carbohydrates	166·3	„
Calcium	0·146	„
Phosphorus	0·649	„
Vitamins	Very poor	

The baby weighed 2,200 grm. and its cord-blood calcium and phosphorus were 8·1 mgm. calcium, and 4·2 mgm. phosphorus per 100 c.c. of the serum. It presented unmistakeable signs of fœtal rickets. The mother's blood calcium was 5·4 mgm. per 100 c.c. of serum and phosphorus 2·9 mgm. per 100 c.c. of serum.

The mother had definite signs of a mild tetany but no clinical signs of osteomalacia. She had slight secondary anæmia (Hb. 66%). She was treated with irradiated ergosterol and good food, and by the time she left hospital her blood calcium was up to 10·2 mgm., and her blood phosphorus 4·2 mgm. per 100 c.c. of serum. After leaving hospital she took 25 mgm. of irradiated ergosterol spread over a month. Her diet was little improved, but she moved to a better and sunnier house and had no further illness. She also took care to eat what she could get. She was readmitted to hospital on July 12, 1933, and was delivered of a living female child weighing 2,315 grm., which showed no signs of rickets, and whose cord blood contained 11·0 mgm. of calcium and 5·16 mgm. of phosphorus. The mother's blood picture was normal and her calcium figure 9·51 mgm. per 100 c.c. of serum.

Case II.—Mrs. W. M. C., Hosp. No. 23784, a Chinese woman, first came to the Peiping Union Medical College Hospital in her fourth pregnancy and was delivered in April 1929 of a living, healthy child.

She came in again for another delivery in February 1932, having had several attacks of diarrhœa during the pregnancy, the last one being at eight months and lasting a month. It

was noticed when the child was born that the head was soft, with very large fontanelles. On an X-ray examination it was found to be suffering from fœtal rickets. It nearly died of melæna neonatorum, but recovered and, under treatment, was reared, but in 1933 still presented signs of healing rickets.

The patient came in again in September 1933. Her blood calcium was 8·9 mgm. and her blood phosphorus 1·54 mgm. per 100 c.c. of serum. On October 13, 1933, she was delivered spontaneously of a 2,635 grm. female child. Apparently the child was healthy, and roentgenograms showed no evidence of fœtal rickets. Its cord blood contained 10·5 mgm. calcium, and 3·63 mgm. phosphorus per 100 c.c. of serum. For a couple of days it did well, then rapidly failed, and died of an unknown cause. A very careful autopsy revealed no sign of rickets in the infant. The mother's diet had been poor, though not as bad as in the first case, and she was getting about 1,000 to 1,200 calories a day before the birth of her baby with fœtal rickets. Between this pregnancy and the last she had been taking more care about food and sunshine, though she was still not sufficiently alive to the dangers attending carelessness in this respect.

In both these cases we have women who have, in the matter of diet, been living near the starvation-line. In neither of them were there any frank osteomalacia symptoms, but in both cases the mother's blood figures for phosphorus and calcium had fallen considerably below the normal. Both of them, during the pregnancies

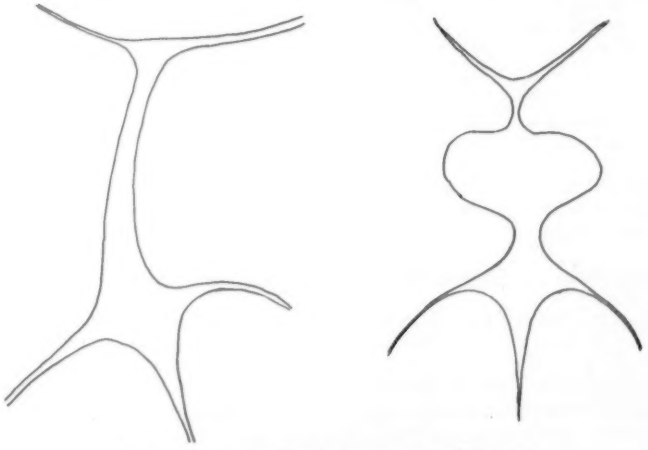


FIG. 21.—The fontanelles in two cases of fœtal rickets.

which resulted in the birth of a child suffering from antenatal rickets, had been troubled by attacks of diarrhœa and anorexia. And it raises a very definite question as to whether the diarrhœa was *due* to avitaminosis, or whether the diarrhœa interfered with the absorption of vitamin D. Probably both suppositions have an element of truth in them.

Do these children born with fœtal rickets present any special peculiarity about the cranial bones? In several of our cases we have had most striking enlargement of the fontanelles, so that the anterior and posterior fontanelles fuse. Two examples of this are shown from our cases of fœtal rickets (fig. 21). This is as it should be, for during the first six months of life the head is said to be specially affected in rickets.

There are two other physical peculiarities exhibited by newborn infants the subject of fœtal rickets, which Dr. A. P. Black has kindly pointed out to the writer.

The first of these concerns the shape of the chest. Compared to that of a normal infant, the chest in these children is markedly flattened at the sides, giving an almost box-shaped chest. This seems to be partially dependent on the want of rigidity which is present at the costochondral junction, and which allows the ends of the ribs to come forward more than is usual (fig. 22).

The second is one which concerns the lower end of the fibula. It has been pointed out that in infantile rickets the lateral outline of the malleolus is not even, but has a small hollow in it. This is due apparently to a hyperplasia at the place of junction of the epiphysis, and also to a prominence of the cartilage of the distal portion of the epiphysis. It is peculiar to rickets and is found in our cases of fœtal rickets.

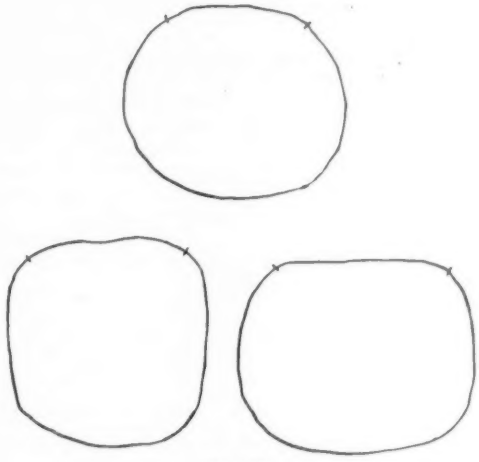


FIG. 22.

In the paper published in 1925 on "Osteomalacia in China" [24] some analyses of fœtal bones from children born to patients with osteomalacia were given. Fœtal rickets was not, apparently, present in these cases.

To compare with these figures, Dr. S. Wan, of the Department of Biochemistry has kindly analysed for me some bone from an infant with definite fœtal rickets, born dead by Cæsarean section from an active case of osteomalacia.

The figures work out as follows :—

	Fresh weight femur grm.	Dry weight femur grm.	Ash weight femur grm.
Normal (average) ...	19·34 ...	5·80 ...	2·53
Fœtal rickets case ...	19·34 ...	5·24 ...	2·04

	Moisture per thousand	Organic matter per thousand	Ash per thousand
Normal (average) ...	699·25 ...	168·41 ...	132·09
Fœtal rickets case ...	728·80 ...	165·57 ...	105·63

	Calcium per thousand of ash	Phosphorus per thousand of ash	Calcium per thousand of bone	Phosphorus per thousand of bone
Normal (average) ...	362·24 ...	185·47 ...	44·71 ...	22·04
Fœtal rickets case ...	323·00 ...	175·40 ...	34·10 ...	18·60

It will be noted that the figures for the case of fœtal rickets are all smaller, with the exception of the figure for moisture per thousand.

Tetany of the uterus.—This is not a question of the tetanic contraction which occurs in obstructed labour. Hess [7], in speaking of tetany speaks of what has been called cardiac tetany in infants and describes a case in which "the heart was found in systole and of the consistency of wood."

Tetany may also affect various involuntary muscles of the body, such as the muscle of the rectal wall and the sphincter ani.

But it appears from the following cases, that in patients with very low calcium and phosphorus, it is possible to get an actual condition of tetany of the uterus leading to the death of the fœtus *in utero*.

Mrs. C. T. L., Chinese, Hosp. No. 38644, was admitted to the Peiping Union Medical College Hospital on December 26, 1932, on account of very marked osteomalacia. She was pregnant, a month from term, and was in considerable distress from attacks of tetany. Blood calcium 4·65 mgm., blood phosphorus 3·15 mgm. per 100 c.c. of serum.

Her measurements were as follows:—

Interspinous	22·5 cm.	Fractures of pelvis and right femur.
Intercristal	26·5 „	
External conjugate	18·0 „	
Interischial	6·5 „	

It was clear that nothing except a Cæsarean section could be done.

Under calcium treatment the tetany diminished somewhat, and an injection of calcium gluconate was given. This procedure for some unexplained reason set up a sharp attack of tetany, and the child died after an hour or so in utero.

Cæsarean section was done about ten hours after the commencement of the attack, as it was thought from the feel of the uterus that an accidental hæmorrhage had occurred. The uterus was tense and tender, the fœtal parts could not be felt, and the patient was showing signs of shock.

On opening the abdomen the uterus presented. It was in a state of tetanic contraction, the waters unruptured.

The tension was so high that on opening the membranes, liquor amnii spurted out to a height of three to three and a half feet. The child was dead, the placenta in position and not detached. There was no accidental hæmorrhage. The incision in the uterus tended to gape, and was closed with a little difficulty. The tubes were cut and tied. The mother made a good recovery and under further treatment lost her pains; the calcium and phosphorus figures rose slowly to the normal, and she left hospital well.

Before this patient left hospital another patient came in:—

Mrs. W. C. C., Chinese, Hosp. No. 39506, in her third pregnancy, and in the seventh month. She was in considerable distress, and had a curious history of quasi-epileptic attacks. Two previous pregnancies had ended at the fifth and sixth months by the death of the child *in utero* during these attacks, and its subsequent delivery.

She had not got marked osteomalacia, but she had osteoporosis and possibly the commencing symptoms of osteomalacia. Under the care of Dr. S. H. Liu she steadily improved, and two months after began to show signs of coming into labour. On account of the findings she was again carefully measured, and it was found that in spite of her steady progress under treatment, pelvic contraction had been progressing and her transischial diameter had diminished from 9 cm. to 6 cm.

When she came in her blood calcium was 3·6 mgm. and her blood phosphorus 2·2 mgm. per 100 c.c. of serum. It was clear that she was suffering from severe tetany and it is likely that both of the previous miscarriages may have been due to tetany of the uterus. There was no other obvious cause for the death of the fœtuses and their being cast off. Under treatment she steadily improved and a living healthy child was delivered at full term by Cæsarean section. The child had no signs of fœtal rickets.

Special Note on the Teeth in Fœtal Rickets (*Dr. J. J. Wolfe*).

The material studied consists of teeth in the lower jaw of two cases of fœtal rickets which came to autopsy, and also teeth in a case of fœtal rickets which came into the Pediatric Ward at the age of 20 months.

This latter case will be dealt with first. It is the only instance, as far as is known, of a case of definite fœtal rickets in which one has had the opportunity of studying the teeth later on, and demonstrating the accuracy of the first diagnosis by the appearances of the erupted teeth (figs. 23 and 24).

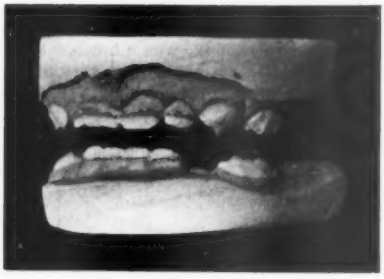


FIG. 23.

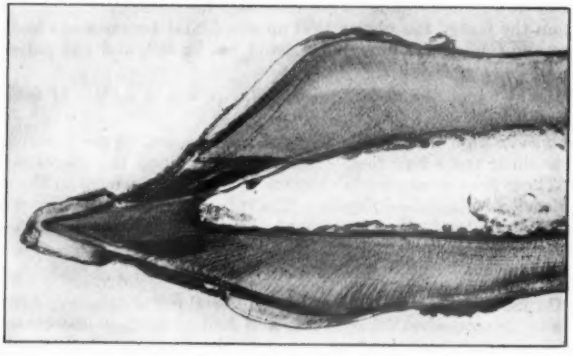


FIG. 24.—Fœtal rickets: section of affected tooth.

Models were made from the impressions of the teeth of Ching Ming (Hosp. No. 35880). They show that there is marked hypoplasia, almost aplasia, of the enamel of the occlusal surface of the molar, and tip of the the canine teeth. The tips of the central and lateral incisors are well formed, hence calcification apparently began normally at the seventeenth week (as is seen also in a section of the central incisor), and proceeded till about the twenty-third week of intra-uterine life. From this period until birth the calcification of the enamel, as manifested by the extreme hypoplasia, was extremely poor. The child was given adequate diet within the first few days of life, and the result is the formation of normal enamel onwards.

When one comes to look more closely at the microphotograph of a ground section of this central incisor, previously mentioned as having been extracted, one sees that normal enamel is present at the tip of the tooth merging gradually into an extremely defective structure. Normal enamel is seen to begin abruptly, however, on that part of the tooth which calcifies in the first month of life. This rapid response of the enamel organ to improvement in diet is in accord with the findings of Mellanby [27] in her experimental rickets in puppies. It can be prognosticated, moreover, that the first permanent molar teeth will show hypoplastic changes in the enamel of occlusal surfaces, and it is clear that the diagnosis of fœtal rickets made at birth was correct.

Secondly: When one studies the sections from cases of fœtal rickets who died at or shortly after birth, one finds the following significant appearances. In sections of the bone of the maxilla of Hosp. No. 37465, wide zones of osteoid tissue, typical of rickets, are seen. In a decalcified section of an incisor tooth from the same case the dentine is seen to be unevenly calcified throughout, the line of calcification is extremely irregular and the predentin layer is much wider than normal. Islands of calcoglobulin are seen scattered along the zone of calcification. In a tooth from Hosp. No. 38841, similar changes in the dentine are seen and in a ground section from the same case rows of interglobular spaces are seen beneath the enamel. The calcifying zone in the dentine is very irregular. Again, from these findings it is clear that the diagnosis of fœtal rickets is confirmed by the sections.

Taken together, these observations accord completely with the other clinical and microscopical findings proving the existence of true fœtal rickets.

(*A fuller account of this work will be published in due time.*)

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Discussion.—Professor EDWARD MELLANBY said that Mrs. Mellanby and himself had never been able to produce fœtal rickets in animals, but they had produced osteoporosis. There was no doubt that fœtal rickets, adult rickets and osteomalacia were the same disease in a sense, but the ætiology was rather different. For osteomalacia to occur there must be more than a deficiency of the calcified vitamins; there must be a real deficiency of phosphorus as well as of vitamin D.

Dr. DONALD HUNTER: In England to-day osteomalacia is a rare disease. Two types are found. The first is due to a diet deficient in vitamin D and calcium salts. It occurs as a result of the industrial depression in the North. One such woman, aged 33, was born in Darlington, Durham, and had always lived there. In 1922, immediately following her fourth pregnancy, she began to have pains in the left hip and back. By 1928 the total height had diminished by two inches, the limbs were bowed, the bones tender, and she was unable to walk unaided. The pelvic measurements were: interspinous 25·4 cm., intercristal 28 cm., external conjugate 16·5 cm., transverse diameter at outlet 2·5 cm. The serum calcium was 9·6 mgm. per 100 c.c., and the plasma phosphorus 1·5 mgm. per 100 c.c. The calcium output was estimated in the urine and fæces for three three-day periods, the patient being kept on a weighed diet of known low-calcium content. The calcium output in urine and fæces was slightly less than in the control. Radiograms of the bones showed definite diminution in density with multiple spontaneous fractures. The calvaria showed innumerable pale, rounded, mottled shadows, many of them more than 1 cm. in diameter. There was a greatly deformed tri-radiate pelvis with fracture of the superior ramus of the os pubis on each side. A piece of bone removed from the inner aspect of the right tibia showed the abnormally deep osteoid zones of osteomalacia, associated with great osteoporosis. She was given a diet of high calcium content, together with large doses of calcium lactate and tablets containing vitamin D. Within three months the pain disappeared from the bones and she began to walk. Within six months she was able to get about the house, to climb the stairs unaided, and to do her usual household duties. Radiograms of the bones showed union of many of the fractures, and complete healing of the defects in the calvaria.[1]

The other cause of osteomalacia is idiopathic steatorrhœa (Gee's disease). This disease occurs in both sexes, and the history nearly always goes back to early childhood. The following features may be present: fatty stools, dilatation of the colon, tetany, osteomalacia, anæmia, skin lesions, and infantilism. These manifestations develop in spite of an adequate diet. We must therefore suppose that there is some disturbance of gastro-intestinal function resulting in deficient production, absorption, or utilization, of one or more essential factors. In fifteen cases recently investigated[2] steatorrhœa and disturbances of calcium metabolism were alone common to the whole group. Changes in the skeleton were found in all cases investigated. Radiograms of the bones showed diminution in density, together with the deformities of osteomalacia. In three cases histological examination of portions of bone showed osteomalacia and osteoporosis. It would therefore appear that osteomalacia may occur not only in persons deprived of calcium salts and vitamin D, but also in others with a defective mechanism for absorption or utilization of these substances.

Dr. V. KORENCHEVSKY said Professor Maxwell's observations showed (1) that the causes of rickets and osteomalacia in China were chiefly deficiency in vitamin D and calcium; (2) that there was no essential difference between rickets and osteomalacia, the latter being the manifestation of rickets in adults: (3) that the blood of rachitic mothers was often poorer in calcium and phosphorus than that of children borne by these mothers.

[1] Hunter, D., and Turnbull, H. M., *Brit. Journ. Surg.*, 1931, xix, 277.
[2] Bennett, I., Hunter, D., and Vaughan, J. M., *Quart. Journ. Med.*, 1932, N.S. i, 603.

These clinical observations were in complete agreement with the following results of his (the speaker's) experiments on rats, published from 1922 to 1924 ("The Ætiology and Pathology of Rickets from an Experimental Point of View," *Med. Res. Counc. Spec. Rep. Ser.*, No. 71, 1922; *Biochem. Journ.*, xvii, 597; xviii, 1308): (1) Typical rickets was produced by a diet deficient in fat soluble vitamins and calcium in young rats and, using the same diet, a picture typical of osteomalacia was produced in adult rats.

(2) At the day of birth the water, calcium phosphorus and nitrogen content in the young was nearly the same, irrespective of the deficiency or abundance of fat-soluble vitamins in the diet of the mother during pregnancy. However, deficient diet of the mother during pregnancy influenced the young in other respects. The young from deficient mothers developed more severe rickets than those from normal rats. The litters were smaller in number, and the number of young born dead or weaker and eaten by the mothers was greater (*Biochem. Journ.*, xvii, 597). At the same time the skeleton of these mother rats was found to be poorer in calcium (see *Med. Res. Counc. Spec. Rep.* 110) than that of normal rats of the same age and showed osteomalacia or osteoporosis.

The normal chemical composition shown to exist at birth in fœtuses born of mothers kept on a diet deficient in fat-soluble vitamins was explained by the fact that the maternal organism would, as far as possible, yield all the necessary substances to the offspring by the sacrifice of its own tissues. Another case of maternal sacrifice caused by general fasting of the mother during pregnancy was clearly shown by Rudolsky in 1893 (Dissertation: Petrograd; ref. Korenchevsky and Carr, *Biochem. Journ.*, 1924, xviii, 1313).

Dr. H. B. Fell: Is there any histological difference between the osteoid tissue in fœtal rickets and the osteoid tissue of the normal fœtus? I ask this question because Miss C. F. Fischmann, one of my colleagues at the Strangeways Laboratory, finds that there is a marked difference between osteoid tissue formed *in vitro* by osteogenic tissue grown in vitamin D-deficient medium and the osteoid tissue formed by similar cultures grown in normal medium.

Miss L. Wills said that in connexion with the question of osteomalacia being low-calcium rickets in the adult, it was interesting to note that in Bombay tetany was a rare complication of osteomalacia and that blood analyses showed that the majority of the cases had very low inorganic-phosphate figures, the serum calcium being only slightly reduced. Osteomalacia in Bombay, therefore, more closely resembled infantile rickets as commonly seen in this country than did Professor Maxwell's low-calcium osteomalacia cases.

Mr. V. B. Green-Armytage said that the whole tropical world owed a debt of gratitude to Professor Maxwell and his collaborators for their biochemical research on osteomalacia which only those who had an intimate knowledge of the difficulties besetting such work in the tropics could fully appreciate. The clinical aspect of this disease was not perhaps so easily recognized as would appear from the photographs shown this evening since he (the speaker) considered that there were five common clinical types which might or might not dovetail into one another. In the first the symptoms were almost entirely gastro-intestinal; in the second they were those of severe anæmia and tetany only; in the third the symptoms were mainly those of rheumatism and of joint pain or stiffness. In the fourth the lower motor neuron and sympathetic system was mostly involved, whereas in the fifth, and most easily diagnosed, the lesions were obviously osseous.

In his experience as to the acuteness of symptoms and the combination of these clinical types, much depended upon the presence of added oral or intestinal sepsis.

He had seen great numbers of cases of neonatal rickets and a smaller number of prenatal rickets, but his impression was that these features in the infant very much depended upon whether the disease in the mother was acute or chronic. In his experience pre- and neo-natal rickets were only met with if the maternal osteomalacic symptoms were acute.

He had observed that these infants were wizened and thin and very liable to suffer from hæmorrhage from the rectum or subcutaneously and that at the time of Cæsarean section the omentum of the mother was so shrivelled (due to absorption of fat) that it could not be found or brought down. Another feature of the operation was that, despite the lack of calcium, there was never any post-partum bleeding or difficulty in controlling the uterus at laparotomy. Owing to the gross deformity of the lower limbs so often met with, he considered that the ideal Cæsarean incision was the fundal one described by McCann. With this incision there was little hæmorrhage and far greater ease of approach.

He was particularly interested in Professor Maxwell's remarks on the funnel pelvis, because for years he had been teaching that, just as in this country some pregnant patients complained of vitamin A and D deficiency symptoms—such as insomnia, tetany, joint pains, cramps, rashes and pains referred to the "gliding" symphysis—so in others at or about the time of puberty, there were signs if looked for, of alteration of the outlet of the pelvis with the typical funnel deformity, which was perhaps more likely to be seen now than hitherto, in the northern depressed areas of Great Britain. In a consecutive series of 3,000 labour cases in European and Anglo-Indian communities he had found a pelvis with an outlet less than $3\frac{3}{4}$ in. in 67, the other measurements being normal. There was just one question of some interest he would like to ask Professor Maxwell, and that was, whether he had observed a greater tendency to eclampsia in his acute or chronic osteomalacics, as compared with the ordinary toxæmic patients met with during pregnancy in China. The reason he requested this information was that out of hundreds of cases of osteomalacia, many of them with gross albuminuria and anæmia, he had no memory of one in which eclampsia had developed. The question was one of some importance, because there were many who considered that the preventive treatment of eclampsia and toxæmia was mainly that of the diet and the exhibition of calcium in large doses. If that was so, it seemed strange that in a condition like osteomalacia in which there was invariably an obvious large defect in the calcium and phosphorus content of the blood-serum, eclampsia should be practically unknown. It would be illuminating to hear Professor Maxwell's experience.

Dr. G. W. THEOBALD said that the two points in the paper which struck him most were: (1) The percentage of serum calcium in patients suffering from osteomalacia varied within wide limits, and women with osteomalacia sometimes had a higher percentage of serum calcium than others without symptoms of the disease. (2) The fœtal blood contained a higher percentage of calcium than the maternal. The first point indicated that calcium was present in the blood in various forms and that estimations of the percentage of total calcium in the blood was of relatively little value in calcium-deficiency diseases. The second showed that the fœtus was a true parasite and robbed the mother of substances she could ill-afford.

Dr. MAXWELL (in reply) said that with regard to several of the points raised in discussion, such as the question of osteoid tissue and the rarity of the coexistence of œsteomalacia and eclampsia, he was unable to give definite answers. It was his impression that osteomalacia and eclampsia were rarely found together, but on his return to China he would pay special attention to this point. The whole subject contained many unsolved questions and he hoped to deal specially with some of these in the future.

Section of Physical Medicine

President—J. BARNES BURT, M.D.

[*November* 16, 1934]

DISCUSSION ON SHORT-WAVE DIATHERMY

OPENING PAPERS

I. Dr. W. J. Turrell

ABSTRACT.—It is submitted that the thermal action of short-wave therapy does not account for the therapeutic results obtained.

The theory is put forward that many of the results obtained can be better explained by the disruptive and dispersive action of the impact of the electromagnetic vibrations. An analogy, indicating such disruptive effects at high frequency, is drawn from the molecular vibrations—transmitted through transformer oil, and excited by the application of high frequency currents to the layers of quartz in the piezo-electric oscillator of quartz.

It is submitted that these disruptive and dispersive effects will be greatest where the conductivity of the tissues is low, such as in bones and fat, and it is shown that it is in these regions that the therapeutic action of these currents is most obvious. It is also pointed out that, if effects, comparable to those obtained in the subcutaneous area, are obtained in the deeper tissues and organs, the application of deep-wave therapy would be attended by serious risk.

RÉSUMÉ.—L'auteur soumet que l'effet calorifique seul des ondes courtes ne suffit pas à expliquer les effets thérapeutiques actuellement obtenus.

Il émet la théorie que beaucoup de ces résultats peuvent mieux s'expliquer par les effets disruptifs et dispersifs résultant du passage des ondes électromagnétiques. Il cite comme cas analogue les effets des vibrations à haute fréquence produits par l'application de courants à haute fréquence à des lamelles de quartz et transmises par de l'huile de transformateur.

Il soumet que ces effets disruptifs et dispersifs seront au maximum là où la résistance électrique est la plus grande, comme dans les os et dans la graisse, et il montre que c'est, en effet, dans ces régions que l'action thérapeutique de ces ondes est la plus marquée. Il montre aussi que, si les effets obtenus dans les tissus plus profonds sont comparables à ceux obtenus dans les tissus sous-cutanés, l'application de la thérapie à ondes courtes serait accompagnée par de graves dangers.

ZUSAMMENFASSUNG.—Es ist vorgelegen dass die Erfolge der Kurzwellentherapie nicht allein durch die Wärmeentwicklung zu erklären sind.

Die Theorie ist vorgebracht dass viele der Erfolge besser durch die disruptive und dispersive Wirkung der elektromagnetischen Wellen erklärt werden können. Als Beispiel solcher disruptiven Wirkung gibt Verf. die Resultate der durch Hochfrequenzspannung in Quarzplatten erzeugte, und durch Transformator-Öl fortgepflanzte Hochfrequenz-Wellen.

Es ist vorgelegen dass diese disruptive Wirkung am grössten sein wird da wo der elektrische Widerstand der Gewebe am grössten ist, z.B. in Knochen und Fett, und es ist gezeigt dass die therapeutische Wirkung dieser Wellen gerade in diesen Teilen am merkbarsten sind. Verf. weist auch darauf hin, dass wenn in tiefer gelegenen Gewebe und Organen Wirkungen erzielt werden, die denen in den subkutanen Geweben bemerkten ähneln, so wird die Kurzwellentherapie mit ernster Gafahr begleitet sein.

Our subject this evening, short-wave therapy, is particularly suitable for discussion, for it is, in a limited sense, a new subject, and is consequently one in regard to which our opinions must be in a state of flux, and, however dogmatically we may assert them, they must be subject to correction and revision.

In these introductory remarks a short account of the fundamental principles involved is called for.

Short-wave therapy covers a relatively brief space in the extensive range of electromagnetic vibrations. The diathermy wave-length of about 300 metres corresponds approximately with that of the London Regional broadcasting centre, and short-wave therapy employs a wave-length co-extensive with that of the short-wave wireless stations, 3 to 30 metres.

Throughout the whole range of known electromagnetic vibrations, extending from the longest Hertzian to the shortest cosmic waves, there is no breach of continuity, and, so gradually does the distinction, which we draw between the action of adjoining wave-lengths, merge into its neighbours, that it is impossible to state where one begins and the adjoining ones leave off. Nowhere, in fact, can the truth of the old dictum, "Nihil per saltum Natura fecit," be better exemplified.

It would seem that the basic or fundamental action of all electromagnetic vibrations is that of a blow or impact, as Professor Sir James Jeans has recently stated in speaking of the "frameworks along which our minds receive their whole knowledge of the outer world. This knowledge comes to our minds in the form of messages passed on from our senses: these in turn have received them as impacts or transfers of electromagnetic momentum or energy."

In attempting to visualize the action of the electromagnetic vibrations, we are surely justified in retaining this dynamic idea of a blow or impact.

It is true that one of the results of this impact is the conversion of the arrested kinetic energy into heat, and, when diathermy was first introduced, we were quite content to attribute its action entirely to its thermal effects. Subsequently, however, it was found that effects ensued from the application of high-frequency currents which could not be attributed solely to its heating action. D'Arsonval showed that the toxicity of a virulent diphtheria toxin could be destroyed by high-frequency currents, although the temperature of the medium did not exceed 98·5° F. Other observers, working independently, came to the similar conclusion that the effects that they observed, such as the rapid disappearance of ecchymosis and swelling, could not be accounted for simply as the result of thermal action. But, perhaps, the most convincing experiments in this connexion are those of D'Arsonval by which he established the fact that when administering these currents we are dealing with two entirely different types: (1) A current of conduction, and (2) a current of capacity. This important point was revealed by the difference in heat generated when a high-frequency current of constant intensity was passed through media of varying resistance. The remarkable fact was established that under these conditions high-frequency currents did not obey the Law of Joule. For when a high-frequency current of constant intensity was passed through salt solutions of varying resistance, the following degrees of heat were registered: with a resistance of 13 ohms, 2 degrees were registered: when the resistance was increased to 1,500 ohms, the maximum heat of 86 degrees was obtained: but when the resistance was further increased to 35,000 ohms, the heat fell to the 2 degrees which was originally registered with a resistance of 13 ohms.

When employing more complex media than salt solutions, a lower degree of heat was obtained. D'Arsonval explained these phenomena by stating that "the sides of the containing vessel and the liquid interposed between the electrodes constitute not only a resistance, but also a condenser which heats up in accordance with the phenomena of hysteresis or of the dielectric viscosity at these frequencies."

These phenomena and conclusions are of fundamental importance in the study

of short-wave therapy, and their value is greatly enhanced by the fact that they are not *ad hoc* experiments, for they were published by D'Arsonval in 1927, considerably prior to the advent of short-wave therapy.

The dynamic, disruptive, pounding action must be more in evidence in these capacity currents, than when the current flows freely through a good conducting medium, and the electromagnetic stresses must be greater in the former case.

A high-frequency current will flow more readily by a path of good conduction than by a path of high dielectric hysteresis. This is well illustrated by the following unfortunate occurrence. Once upon a time, an electrotherapist was treating a nævus in a child by electrocoagulation. The child was placed on the condenser pad of Bordier, which consists of an underlying copper gauze electrode covered by an overlapping sheet of asbestos. The asbestos sheet, when dry, forms a very efficient dielectric of high viscosity. Unfortunately, during the operation the child passed water and so wetted the sheet at one point, thus affording a path of high conductivity to the high-frequency current; at this point the current concentrated, with the result that the child received a severe burn on his buttocks.

When high-frequency currents, of whatever wave-length, are applied to the human body, they encounter the resistance of the skin. Through the skin, especially if it is dry and thick, owing to its high viscosity and hysteresis, the high-frequency currents, as is the case with the glass-containing walls in D'Arsonval's experiments, pass as capacity currents.

The further course of the current is influenced by the nature of the subcutaneous tissues or structures. If these tissues are, as is the case with muscles, well bathed in the highly conductive fluids of the body, the current will be one of conduction. If, on the other hand, there are subcutaneous bony structures or thick layers of fat, the current will be largely one of capacity according to their hysteresis or dielectric viscosity; or as Bordier well terms it, the current will pass as a leaking condenser effect. It is under the latter conditions that we shall obtain the maximum disruptive, dispersive, and pounding action of short-wave high-frequency currents. It is important to remember that, as the wave-length becomes shorter and the frequency increases, the current of capacity more and more replaces the current of conduction, for the coefficient of viscosity increases as the square of the frequency. Consequently, the shorter the wave-length, the more important the nature of the skin and subcutaneous structures becomes, though in the deeper tissues, owing to the high conductivity of the medium which surrounds and permeates them, the current will pass mainly by conduction with wave-lengths, at any rate, not shorter than 6 metres.

Now, in what respect does the biological action of these capacity currents differ from that of currents passing by conduction? I submit that we shall find the answer to this question best demonstrated by analogy with the experiments of Professor A. W. Wood and A. L. Loomis on "The Physical and Biological Effects of High-Frequency Sound Waves of Great Intensity."

The apparatus employed in these experiments was a very powerful one, 50,000 volts and a frequency rate of 300,000 a second. The oscillations were obtained by means of a triode valve. One terminal of the apparatus was connected with a plate of lead, supporting several disks of quartz on which was placed a thin sheet of brass connected with the other terminal, the plates and quartz were immersed in a bath of transformer oil.

The following were among the results obtained: "Though the mercury only registered 25 degrees, the thermometer became so hot at the point at which it was held between the finger and thumb that it had to be released. The heat, of course, is developed by friction between the vibrating glass stem and the skin of the fingers, or rather by the rapid pounding of the transverse vibrations, and becomes unbearable only when the glass is squeezed tightly between the thumb and finger." Blood-

blisters, persisting for several weeks, were formed as the result of dipping a fine glass rod in the bath. Small fish and frogs were killed by submitting them for one or two minutes to the vibrations. "Filaments of living spirogyra were torn to pieces and the cells ruptured." "Red blood corpuscles in physiological salt solution are rapidly destroyed, the turbid liquor becoming as clear as a solution of a red aniline dye." Bordier obtained somewhat similar results by employing a 6-metre wave-length at a far lower voltage. Recently it has been reported that mice have been rapidly killed in a powerful electromagnetic field of 1½ metres, and that flies flying across such a field drop dead. The experiments of Wood and Loomis were not confined to frequencies of 300,000, and it is of historical as well as of scientific interest to note that these workers recorded, more than seven years ago, in the following passage the application of a 3-metre wave-length. "In the case of a mouse killed by an exposure of two minutes between the plates of an air condenser operated at 1,000 volts with a frequency of 100 million, we found that the temperature of the body cavity was over 113° F."

It is evident that this dispersive and disruptive action will be largely governed by the part of the body to which the electrodes are applied. They will reach their maximum effect where there are bony surfaces or dense masses of fat. They will be least where the conductivity of the tissues is high, as in muscles and other tissues that are well supplied with blood and lymph. The lungs, lying in close connexion with the bony thorax and containing innumerable air sacs, would tend to the creation of capacity currents.

The better results claimed for the very powerful short-wave instruments may be partly explained by the greater capacity effect obtained in the tissues as the wave-length decreases. The greater power of these instruments enable a shorter wave-length to be employed with sufficient energy.

Though perhaps incapable of proof in the present state of our knowledge, it is reasonable to infer that the more delicate the structure, either of cells or micro-organisms, the greater would be the disruptive action of short and ultra-short electromagnetic vibrations.

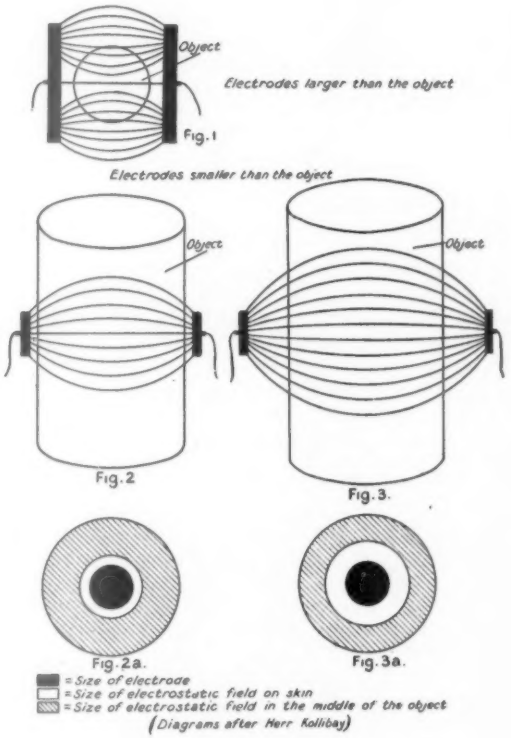
It has been claimed that certain wave-lengths have a specific and a selective action on certain micro-organisms and cells; it will be noticed that these wave-lengths are in the neighbourhood of the shortest wave-lengths which are obtainable with effective energy from the instruments at present available.

It is significant perhaps to note, in relation to the so-called "specific, selective properties for certain cells" of waves up to 4 metres (Schliephake), that it has been stated that, until a frequency of 10^{-6} (30 metres) is reached, the cell membrane is not penetrated by high-frequency currents. It is, moreover, reasonable to infer that the permeability of all cell membranes will not be reached at the same frequency. This would not imply a specific or selective action, but rather a critical frequency beyond which the cell membrane would be more readily and completely permeated. If this is the case, the practical point arises that we should not endeavour to apply accurately a specific wave-length, but rather as short a wave-length as the available instrument will permit.

The claim that certain wave-lengths have "specific selective properties for certain cells" savours far too much of the famous Schearer war hoax, in which it was claimed, as doubtless many of you will recollect, that each organ of the body had its specific wave-length, and that, if a wave of similar length was superimposed, sufficient energy would be developed to actuate a certain pricker, which when in action would perforate waxed paper, so that any organ of the body, or any abscess, or lesion of the organ could be delineated.

The claim for the improved or increased thermal action of these short waves, compared with the longer wave-lengths of diathermy currents, will not bear investigation.

Despite the diagrams which illustrate the pages of short-wave apparatus catalogues, the diathermy currents pass in relatively parallel lines through the tissues; whilst the current applied by the condenser electrodes of the short-wave apparatus passes in one of two ways. If the electrodes are larger than the body to which they are applied, there is a certain concentration of the electromagnetic lines. But, if the electrodes are smaller than the body to which they are applied, which, in therapy is practically always the case except in artificial fever induction, there is a considerable divergence of the electromagnetic lines (see diagrams). Consequently the density of the current is less with the short-wave than with



diathermy. We can, moreover, get far more heat energy from a diathermy machine yielding waves of 300 metres, costing about £40, than from a short-wave apparatus giving 6 metres and costing £200 or more, or probably than from a 3 metre costing £750. The reason for this is that a valve emitting 300 metre-waves has an efficiency of 80%; whereas a valve emitting 3 metres has an efficiency of only 3%. Consequently, if you only require thermal effects, you will be well advised to spend £40 instead of £200 or £750.

A very noticeable phenomenon in the administration of short-wave therapy, and one which certainly tends to negative thermal effects, is the very slight or even total

absence of appreciation of heat during the administration of a short-wave treatment which may be followed by most satisfactory results.

So-called "skin-burns" may unfortunately result from short-wave therapy, in fact I think that far more care is required to avoid them than with diathermy. The absence or only slight sensation of heat which may attend their administration and the difficulty of measuring the current in the patient's circuit tend to their production. Distortion or concentration of the electromagnetic field may produce them. Subcutaneous masses of fat conduce to their occurrence. The main point of interest about these lesions, I hesitate to call them burns, is the manner in which they differ from the true heat burns of diathermy. They are far more painful than diathermy burns, owing to the induration of the surrounding tissues which accompanies them.

I have only actually seen two of these lesions, but they are by no means uncommon, and in the administration of the fever therapy they are said to be sometimes very severe. One of my cases was a hospital patient with a rheumatic knee thickly covered with fat. She was very carefully treated by the spark-gap type of apparatus. After the treatment the skin was distinctly red, but there was no blister and no breach in the continuity of the skin. Subsequently, a small ulcer appeared about ¼ in. square; this was surrounded by a swollen, thickened, indurated area about 3 in. across with two or three indurated transverse ridges produced by constriction of the bandage. The condition was very painful, but the patient made no complaint, as her rheumatism had been quickly cured. The patient on being asked why she did not complain of the heat during the treatment, replied that she did not feel any heat, "only just natural like" to quote her own words.

The other lesion occurred during the treatment of an elderly man for rheumatism of the shoulder, on 6 metres from a valve machine. The lesion was in this case a very slight one, so slight indeed as not to attract the patient's attention. But there appeared on his shoulder two deep red linear marks, which subsequently went through the colour changes characteristic of a bruise. There was no ulcer, blister, or breach of skin continuity. The lesion appeared to be due to disruptive action rather than to heat. Other observers have remarked that blood is extravasated from the veins after treatment by 10-metre wave-lengths or less. An erythema of the skin following diathermy quickly disappears, but the redness of the skin produced by short-wave therapy persists for some days. The former is a vasodilator effect due to heat, the latter is occasioned by extravasation produced by the pounding action of the capacity currents in the skin area.

I have attempted to approach the subject of short-wave therapy from the point of view of its underlying principles, and I do not wish to bore you by the enumeration of miraculous cures. I would merely summarize my successful results by stating that they have occurred under such conditions as would indicate a capacity current effect. In many cases this would merely be the result of a titivation or perturbation in the superficial tissues causing a dispersal of recent inflammatory exudation. In other cases a more powerful current actuating a shorter wave-length would result in a disruptive action on such conditions as superficial abscesses, boils, or carbuncles, and possibly on the specific microörganisms themselves which have a causal relationship to these conditions.

I would, moreover, like to record the surprisingly quick, or almost immediate results that are obtained by short-wave therapy in certain cases. I have certainly not observed such immediate results from any other form of physical treatment, and I am of opinion that most of these results can be explained by the dispersive action of capacity currents upon recent effusions. Perhaps the most striking objective results are to be seen in the treatment of certain forms of varicose ulcers; the marked vascular engorgement and the subcutaneous induration, which ensues upon the treatment of these conditions frequently necessitates intermission of the application.

One is led to think that, if similar, or, as is often claimed, greater, changes take place in the deeper tissues and organs, short-wave therapy cannot be free from risk.

In conclusion I would like to express my firm belief that the advent of short-wave therapy opens up a field of treatment of great possibilities hitherto totally unexplored.

II. Dr. Albert Eidinow

The biological action of the high-frequency current varies with the wave-length and the frequency of oscillation. Following the work of D'Arsonval, it was found that the high-frequency currents above 300 metres in length which are utilized in medical diathermy caused heating of the tissues. With the advance of knowledge and progressive technical research it has now been possible to produce high-frequency currents emitting wave-lengths as low as 1·9 metres.

It is claimed that there are marked differences between the biological action of the diathermy current and that of the ultra-short high-frequency current. With the diathermy current the electrodes must be in direct contact with the surface and the conducting current passes from one electrode to the other. The heat produced varies in the different tissues according to their electrical resistance.

With ultra-short high-frequency currents the capacity of electrical charge in the condenser field determines the degree of biological reaction. Within certain limits, intensity of reaction depends upon: (1) Frequency and wave-length; (2) electrical output, amperage, voltage—i.e. wattage of apparatus. The tissues placed in the condenser field are balanced with the resonance of the electric field and discharged through the dielectric media. Therefore the amount of heat generated depends upon the specific inductive capacity of the tissues and the dielectric medium through which it is discharged. It is claimed that for this reason ultra-short waves can be localized and can penetrate to the depth of the tissues and even to the molecular particles of living cells. The final physiological action of high-frequency currents is heat. It is, however, claimed that, apart from heating effects, ultra-short waves of certain wave-lengths have specific action on specialized tissue-cells and bacteria.

Low-frequency currents are carried into the tissue-cells and cause electrolytic dissociation of ions. This causes faradic or galvanic reaction, due to stimulation of muscle and nerve-fibres by electrolytes. High-frequency currents cause rapid oscillation and the alternating reversal of the phases of polarity neutralizes electro-chemical reactions in the tissue-cells and causes heat formation. The heat produced by the diathermy current is explained by the basis of the ohmic resistance and electrical conductivity of the tissue cells and fluids. The current flows along the lines of least resistance.

With the surgical diathermy current, the reactions of the tissues are controlled by the regulation of the voltage, the amperage, and the frequency of the current. The correct balance of these factors regulates the capacity-inductance and ohmic resistance of the tissues. The sudden elevation of temperature over and above 42° C. rapidly contracts or expands the tissue cells and causes their rupture, which results in the coagulation of the proteins and the melting of fats, or the final bloodless severing of the tissues.

Two types of apparatus are used for the generation of high-frequency currents. Spark-gap apparatus emits surging or damped high-frequency oscillations. Radiotrom valve apparatus produces rhythmical undamped continuous oscillations free from external air resistance. The final biological effect of both these types of apparatus, provided they have sufficient electrical power, is identical. Wildermuth has determined the specific resistance of the tissues compared with normal physiological saline taken as unity at 18° C. (300 metres.)

The following table expresses his results:—

Fatty tissue ...	... 19·4	Liver	... 2·8—3·3
Brain	... 5·5—6·8	Skin	... 2·5—3·0
Lung	... 3·5—4·0	Muscle	... 1·2—1·5
		Blood	... 1·0

The highest resistance, and therefore the greatest heating, occurs in the fatty tissues. The work of Schliephake, Haase, Pflomm and Reiter advances the claim that the ultra-short waves, shorter than 20 metres in length, have fundamentally different action on the human body than any other oscillations of the electromagnetic spectrum. Schliephake claims that: (1) The thermal action is of a special nature affecting small particles: (2) the heating can be localized and made selective in nature: (3) there is a specific action on colloids.

In his researches with Haase he claims that there is specific lethal action on bacteria, and that there is a definite wave-length which has selective action for each type of organism. In addition to this he is of the opinion that toxins are destroyed, antitoxins are activated, and in this way the healing of inflammatory lesions is accelerated.

Liebesny says that actinomycosis is most effectively destroyed by a wave-length of 4 metres. Reiter claims that a wave-length of 3·4 metres is specific for tumour cells. Schereschewsky has shown that it is possible to destroy the Rous sarcoma tumour in fowls and the mouse-carcinoma tumour by means of coagulation necrosis. He claims specific action between 1·5 and 3·4 metres. Gosset has destroyed plant tumour by massive exposure to 3·4 metres (150 million cycles).

Christie and Loomis have carried out extensive research on ultra-high-frequency currents. In their publication in October 1928 they state that the biological effects of electromagnetic waves ranging from 3·4 metres to 1·9 metres in wave-length, or from 8 million to 158 million cycles per second in frequency, can be fully explained on the basis of the heat generated by the induced currents. There was no evidence to support the theory that certain wave-lengths have specific action on living cells. The effects are directly proportional to the strength of the wave-length of the electromagnetic field and vary with the dielectric properties of the tissues.

The work of Westermark was confined entirely to the diathermy high-frequency currents of 300 metres. He carried out an extensive investigation of the biological action of this current on animals, and on the treatment of the Flexner-Jobling's rat-carcinoma and the Jensen rat-sarcoma. He has shown that it is possible to destroy these tumours by heat. If the animals are effectively cooled there is no destruction of the tumours, and it is possible, by careful regulation of the electrodes, to destroy such tumours without producing excessive necrosis of animal tissues. The same facts hold true for the ultra-short waves, for if the body is effectively cooled by means of a current of ice-cold air the heating effects can be completely abolished. The circulation of the blood must play an important rôle in the conduction of heat and will prevent the excessive increase of temperature in localized parts of the body. With the heating of the tissues immediate vasodilatation results. With excessive heating there is coagulation of the blood-vessels, mainly due to the coagulation of proteins (S. fibrinogen). When the blood-circulation is arrested the heat effect is localized within the tissues, and necrosis will be produced. With ultra-short waves fatty tissues appear to be most rapidly heated; Dr. H. J. Taylor has demonstrated this to me. Fats can be made to melt very quickly when placed in the condenser field and exposed to ultra-short waves of 4·5 and 3·4 metres. An emulsion of fat and gelatin in a solid block can be made to disintegrate with the greatest rapidity.

In my experiments I have studied the effect of ultra-short waves of 4·5 metres and 3·4 metres on bacteria and blood, as tested in the living animal *in vivo* and *in vitro*. I may summarize the results of my experiments by stating that I have been

unable to demonstrate any bactericidal action whatsoever with these wave-lengths, provided that the tissues were effectively cooled. In my first series of experiments I placed some sterile gauze soaked in a broth emulsion of *B. coli*, staphylococci, streptococci and the *Micrococcus catarrhalis* under the skin of normal rats, over the right or left flank. The skin-area over the site of the insertion of the gauze was exposed to ultra-short waves of 3·4 and 4·5 metres, and intensive exposures were given so that the animals died soon after exposure. The pieces of gauze were removed and it was found that the bacteria had survived (fig. 1). The effect of exposing animals to ultra-short waves is to produce an immediate intensive hyperæmia with massive dilatation of the blood-vessels. More intensive exposure produces necrosis of the tissues, and the zone of necrosis follows the direction of the ultra-short waves between the electrodes. If the right flank of an animal is exposed, the skin

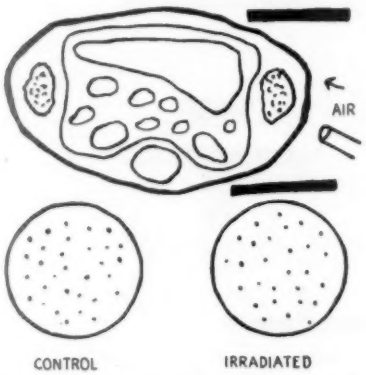


FIG. 1.—Exposure of gauze and bacteria under skin of rats.
U.S.W. = 4·5 + 3·4 metres.

shows the greatest damage, but there is necrosis which passes right through the abdominal wall and peritoneum.

Isolated areas of necrosis are seen in the abdomen, along the edge of the liver, the upper pole and edge of the kidneys, and isolated areas of the bowels which are distended with gas. This effect is due to discharge and greater electrical capacity concentrated in these areas. The sections under the microscope which I have demonstrated show the immediate effects on the skin and liver of a rat that was killed an hour after exposure to ultra-short waves of 3·4 metres.

Experiments *in vitro* on whole blood were carried out by exposing the blood in a quartz phial of 2 c.c. capacity to the ultra-short high-frequency field of 3·4 and 4·5 metres (figs. 2 and 3). Working with citrated blood and defibrinated blood, I was unable to find any change in blood fragility or blood-sedimentation rate.

FRAGILITY OF RED CORPUSCLES FOLLOWING EXPOSURE TO ULTRA-SHORT WAVE-LENGTH.

Concent. saline % ...	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9
10 min. 4·5 metres ...	+	+	+	+	+	±	−	−	−
20 min.	+	+	+	+	+	±	−	−	−
10 min. 3·4 metres ...	+	+	+	+	+	±	−	−	−
20 min. 3·4 metres ...	+	+	+	+	+	±	−	−	−
Control normal ...	+	+	+	+	+	±	−	−	−

SEDIMENTATION RATE OF BLOOD EXPOSED TO ULTRA-SHORT WAVE-LENGTH 4·5 + 3·4 METRES.
(Tested *in vitro*.)

	1 hour	2 hours	3 hours
Normal	17	28	32
Ultra-short wave-length 4·5 metres 5′	18	29	34
4·5 metres 10′	18	27	34
Ultra-short wave-length 3·4 metres 5′	17	24	32
3·4 metres 10′	18	26	33

By these experiments it was not possible to demonstrate changes in the nature of the proteins and colloids of blood and serum following exposure to ultra-short waves. This work was carried out with the help of my colleagues Dr. H. J. Taylor and Dr. T. Reiter who kindly exposed the blood samples to the ultra-short high-frequency

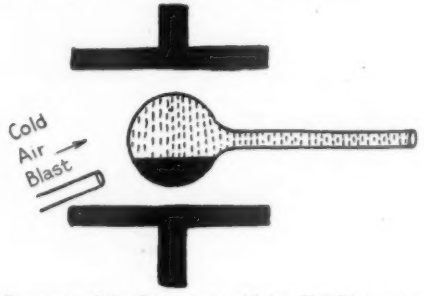


FIG. 2.—Exposure of blood in quartz phial to U.S.W. 4·5 + 3·4 metres.

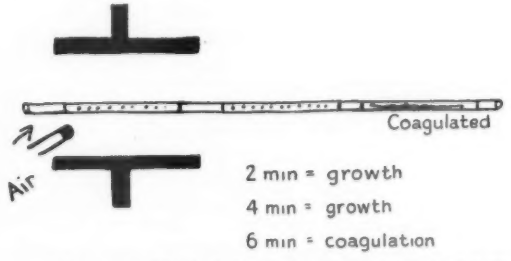


FIG. 3.—Exposure of serum and bacteria in quartz capillary tube to U.S.W. 3·4 metres.

rays. The quartz flask was cooled by means of a current of ice-cold air. It is necessary to use quartz as the ordinary soda glass gets heated in the high-frequency field.

Experiments carried out by the exposure of a suspension of living bacteria mixed with defibrinated blood have in all cases failed to demonstrate any direct bactericidal action and further have failed to demonstrate any change in virulence of bacteria or bactericidal properties of the leucocytes (fig. 4). Apart from the action of heating I have completely failed to demonstrate any biological effect.

My research confirms the observations of Christie and Loomis, and I have failed to find any effect with ultra-short waves of high frequency which could not be produced by the ordinary diathermy current of 300 metres and a frequency of roughly one million cycles.

The effect of the ultra-short waves can be adequately explained by the heating effect, which can vary from a temporary dilatation of the blood capillaries to massive necrosis of the tissues.

The greatest heating appears to be centred in the fatty tissues and this may explain the deeper heating of the ultra-short waves as compared to the diathermy current, and consequently why these rays are of benefit in acute and chronic pyogenic lesions. The fatty content of pus may be heated in the depth of an abscess cavity.

It is claimed that the depth of the heating can be localized and regulated. In my animal experiments I have completely failed to obtain this effect, and the maximum action has always occurred at the surface and depth of the skin. The intensity and energy of the ultra-short-wave apparatus appear to be much greater than that of the diathermy apparatus. This may explain the great advantage of the ultra-short waves as compared to the diathermy current, but a critical analysis of the clinical results and the experimental research makes it doubtful if there is sufficient advantage obtained by the ultra-short waves to warrant the high expenditure for this apparatus.

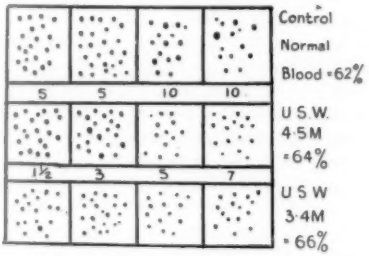


FIG. 4.—Bactericidal power of defibrinated blood exposed to U.S.W. 4·5 + 3 4 metres.

Summary.—(1) Schliephake, Haase, Pflomm and Reiter state that ultra-short waves from 15 to 3 metres have specific biological action, apart from heat.

(2) Christie and Loomis attribute the whole action of ultra-short waves to the heat action.

(3) Experiments which have been carried out *in vivo* and *in vitro* show that there is no specific action on bacteria or tissue-cells. (*a*) Bacteria soaked on to a piece of gauze placed under the skin of animals and exposed to ultra-short waves are undamaged with lethal doses of ultra-short waves. (*b*) There is no change in fragility, sedimentation rate, and bactericidal power of the blood following exposure *in vitro*.

(4) The action of ultra-short waves appears to be coagulative necrosis and extreme vasodilatation, which is similar to the action of diathermy high-frequency currents of about 300 metres.

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III. Dr. Justina Wilson

I have used short and ultra-short waves for nine months in private practice, and for many weeks at St. Mary's Hospital, so a few notes may not be out of place on the therapeutic effects of this, the youngest and most important member of the physiotherapeutic family, whose advent has brought us face to face with many interesting and difficult problems.

First of all, Dr. Turrell has given us food for thought by his remarks. He has also written the first article on short-wave therapy from the English side, and although he has considerably modified his first tentative conclusions, I still disagree with him on some points, and I greatly regret that in that article he leaped so hastily into the arena with that unfortunate title "parathermy."

Could anything be more unlike parathermy than this "through flooding of the tissues" (Schliephake's "Durchflutung"), flooding deep and penetrating, provided the requisite energy or output be behind it, and provided it be applied with adequate insulation and depth in the condenser field.

Provided these conditions be fulfilled we can be sure of obtaining a concentration of heat in any required depth, or we can apply it to superficial conditions without the limitations imposed by fat and skin as in diathermy.

I wonder why Dr. Turrell's capacity currents confine their remarkable "pounding and disruptive action" solely to superficial tissues or to the surface of bones! Surely it is the character and function of capacity currents and currents of displacement not to excite skin and subcutaneous tissues, but to go through all tissues right down to the depths. The lines of force of the current of displacement *must* penetrate every capacity component. In the body where the tissues lie in parallel they do permeate these. Their influence I should not describe as "pounding" or "violent." This is not a bombardment like that by X-rays. There is no disruption of atoms by a current of displacement. Its effect is a vibration of every electron in each atom of every capacity branch traversed by the lines of force. These must penetrate though they may not actually produce heat. That heat will be proportional to (1) the amount of available energy; (2) the excellence and depth of the dielectric.

Burns.—Dr. Turrell dreads burns. I do not. I have given as many treatments as he has done, both in hospital and in private, but I have never seen or heard of a burn occurring. A few simple rules make these impossible: (1) There must be no hidden metal in the patient's clothing; (2) electrodes must never be placed on already damp and perspiring surfaces; (3) with an already high filament voltage care must be taken not to tune the patient's circuit suddenly into resonance, otherwise we get a sudden surge of heat; (4) outstanding parts, such as ears, must be protected; and (5) lastly, and chiefly, we must have adequate insulation with the correct materials and requisite depth.

Machines.—Personally I use valve machines only, because I think the wave-form of the oscillations is important, especially in the ultra-short-wave field, and this must be a factor when effects other than thermal are involved. Smooth oscillations of efficient thermonic valves are more likely to be a factor of importance here than a succession of groups of damped oscillations from the spark-gap.

At present most of the English valve machines seem to be still in the developmental stage. So far, I have found nothing from the point of view of scientific construction, perfect detail, and safety to compare with Siemens' machines, of which there are four types:—

(1) The pyotherm, 1,000 watts, one wave-length of 12. I saw this machine in use at Schliephake's Clinic. The results were extremely good, not only in artificial fever and deep-seated arthritis, but in certain pathological conditions of lung, liver and spleen.

(2) The ultra-pandoros, 650 watts, one wave-length of 15 and nine, continuously

changeable wave-lengths from 6 to 3. In this most useful type the design for generating apparatus is brought to a high degree of perfection. The advantage of being able to vary the wave-lengths within the limits of 6 to 3 metres is that the change of frequency so obtained enables us to get a different heat distribution in a given group of tissues having different conductivities and dielectric constants. It has a very simple but effective arrangement for the change-over to a definite wave-length. Another advantage is the high energy output in the patient's circuit which enables us to treat any section of the body or head with any wave-length from 6 to 3, or to give an efficient general treatment of the whole body.

(3) The well-known radiotherm, 350 watts, two wave-lengths of 30 and 6.

(4) The ultratherm, 300 watts, one wave-length of 6: chiefly used for ears, noses, throats, antra and sinuses.

I began with the radiotherm, which I have installed at St. Mary's Hospital. Its wave-length suffices for most of the hospital routine work, and I get better and quicker results than with diathermy or the constant current in 80 per cent. of cases of rheumatism, sciatica, etc., and extraordinarily good results in inflammatory conditions with suppuration in subacute and even acute cases of inflammation of the antra or sinuses, and the treatment of carbuncles, boils and abscesses. The results are also most encouraging in the treatment of bronchial asthma.

They were so convincing that I felt I must go further and gain experience in the ultra-short-wave field with a machine giving these wave-lengths from 6 down to 3 metres. A second visit to Giessen quite convinced me of this. Schliephake had meanwhile installed the ultra-pandoros and was getting far better results in deep-seated lung conditions and arthritis of the hip, etc., so I got one from Berlin and have never regretted it.

Everyone here of course is convinced of the fundamental difference between long-wave diathermy and short-wave therapy.

In short-wave therapy there is no skin contact: the energy is passed through insulated layers. The part to be treated is in the condenser field. To get the true depth effect, the condenser plates should be insulated by glass cups and by a dielectric of air which can be varied according to the superficial or deep effect desired. This is of extreme importance because, in the condenser field, depth effect is entirely lost if the plates are close to the body. Glass and air are the most satisfying dielectric. If these are difficult or awkward to use, rubber and felt can replace them, provided these are of the right kind and at least 5 to 6 centimetres thick.

In the condenser field we are not dealing with the current of conduction. There is no actual flight or transfer of electrons from one atom to the other, where there is no skin contact, but the oscillations produce in the dielectric a *current of displacement or capacity*. Here the electrons are moved, but not outside their atoms. They are in a state of vibration causing a rise and fall of the lines of force.

In long-wave diathermy the current is confined to the conduction path. The patient is within the oscillating circuit and Joule's law reigns supreme. In the short-wave capacity current there is a much wider and more intense field of action, and as far as the heating effect goes the resistance of the tissues no longer plays the part it did, and if we compare the relative heating effect we no longer find fat, bone and skin are the hottest, and that the heat falls off in the depths. The specific resistance of the tissues does not alter the condenser-field effect, and with adequate power and correct spacing all the different layers can be equally heated. Even in Schliephake's famous bread experiment where sticks of ebonite were introduced as insulators into the dielectric the displacement current of the condenser field was not appreciably affected, whereas in long-wave diathermy the current paths were deflected round the insulator.

Lastly, the outstanding difference between long-wave diathermy and short-wave

therapy is the peculiar effectiveness of the ultra-short wave in infections, and in conditions of suppuration, where diathermy is definitely dangerous. This quality belongs only to the ultra-short waves, from 6 to 3 metres. Between 15 and 30 there is only heat effect.

Still, there are many who say " How about the expenses and the cost of upkeep and running, and what about the chances of breaking a £40 valve? " As a matter of fact, with a valve machine, a fifteen minutes' treatment works out at about 2½d., even allowing for depreciation of the valve, and I am sure that few people realize what it means to have 6, 8 or 10 spark-gaps to contend with—that their faces are easily pitted, with the result that the gap is out of adjustment, and that it costs at least 10s. per gap for smoothing only, without replacement, so that it is not difficult to run up quite a stiff bill for replacements and repairs in spark-gaps.

The question of valves or spark-gap.—This is really a question of the extent and nature of the work to be done. The spark-gap gives a definitely restricted field of application, whereas valve machines are good for both superficial and deep work. Oscillations of 10-30 millions can of course be obtained by both spark-gap and valve, but the valve machine gives us oscillations up to 100 millions, and here the energy is very much higher, up to 650 watts, whereas the best spark-gap at present on the market has an output of only 230 watts which is quite insufficient for deep ultra-short-wave therapy. For deep work in trunk, hip-joint, bony skull, and organs we need a high output and a short wave-length, but the real superiority of the valve is that with it we get a pure spectral line and a definite wave-length—an absolute peak of perfect tuning, whereas in the spark-gap it is always a mixture, a spectral band of various wave-lengths.

I think it was Kowarschik who said that the difference between a valve and a spark-gap was exactly like the difference between monochromatic and polychromatic light. The spark-gap really does not represent true short-wave therapy. It forms an intermediate class which should be called short-wave diathermy, but which gives us a much more penetrating heat than long-wave diathermy.

But there are phenomena here which cannot be explained by thermal effect only. Are these phenomena due, as Turrell suggests, to the pounding and disruptive effect of the more powerful oscillations in the current of displacement? or are they due to some selective influence on cells, colloids, surface membranes of certain tissues? or is there a lethal effect on microörganisms, or do these become so attenuated that the reactive and defensive forces of the body can recover their lost power? Until more work—and more definitely standardized work—is done in our pathological laboratories, and until we can produce some practical measuring instruments which can give us definite information regarding the path of the rays through the tissues, we can only fall back on theories, or else judge by clinical results. These are definitely good.

Time unfortunately does not permit of my telling you more of the encouraging results met with in various fields of work. I will merely now mention an extremely good general treatment by the short waves of the ultra-pandoros, definitely superior to diathermy, whether given by the condenser couch, which results in hot wrists and icy feet, or by Kowarschik's method, which is better but time-consuming.

By the general treatment by the 15 metre-wave, a subnormal temperature can be raised 3° in ten minutes.

I have found this treatment of extreme value in cases of infective arthritis as well as of chronic fibrositis in patients with low temperatures, low red-cell counts and high sedimentation rates. Though every focus of infection has been explored these patients are often unresponsive to other forms of therapy and are a trial to their physicians and a misery to themselves. In all these cases I have found that the temperature rose in ten minutes from about 97° to 99·5°or 100°. All felt extremely fatigued for from six to eight hours after the treatment, but the pains were

immediately relieved. They slept better and then experienced a feeling of well-being which continued for several days. After from six to eight treatments of this kind there was definite improvement in the blood-count and sedimentation rates, and the low temperatures gradually reached the normal. In all cases the striking improvement has been maintained. Four cases of migraine have responded well to this treatment.

In these the general treatment was followed by from ten to twelve minutes' treatment of the brain with a wave of about 4 metres.

In conclusion: It is only by intensive laboratory and clinical work and by close association of pathologists, physicists, and electrotherapeutic physicians that we can form a right judgment regarding the extreme value of these waves for medicine. This is unfortunately difficult to obtain. Medicine is becoming more and more chemical, and less and less interest is taken in physiotherapy; our medical students are still taught nothing definite about its uses, methods, and limitations. It is for us to continue the researches of Schliephake and Esau in Germany, of Liebesny and his co-workers in Vienna, of Izar and Moretti in Italy, and of the French school. If we neglect this, laymen will take it up and they will ruin short-wave therapy for ever in England. Let us see to it then that short-wave therapy is not exploited by unqualified hands, and that we construct, in England, short-wave apparatus adequate as regards both qualitative and quantitative achievement.

Sir Robert Stanton Woods said that there appeared to be ample experimental and clinical evidence that the effects of short-wave therapy were not confined to superficial tissues. It was indeed possible, by varying the wave-length, to eliminate most of the effects on these, although our knowledge of the relationship between depth of effect and conditions of exposure, was, as yet, very imperfect.

Referring to Dr. Eidinow's bactericidal test, his (Sir Robert's) criticism was that the choice of wave-length (3·5 and 4·7 metres) was a purely arbitrary one. This introduced the whole question of selective effect in relation to wave-length. There would appear to be no doubt of the existence of such selectivity but nothing definite with regard to it was known, and the fact that these two wave-lengths were not lethal to the microörganisms must not be interpreted as evidence against such influence on the part of the remainder of a comparatively wide range.

He thought it necessary to voice a warning against the employment by unqualified persons of this potentially dangerous physical agent.

Dr. Douglas Webster said he would not discuss some of the more theoretical aspects of the subject which had been dealt with by Dr. Turrell and Dr. Justina Wilson, but would give some clinical results after six months' working with a short-wave apparatus. He thought that Dr. Justina Wilson's depreciation of the spark-gap apparatus was not justified, and was at least a premature decision. The multiple spark-gap type of ordinary diathermy apparatus had been developed in America, and he had used a short-wave one of this type (by Stanley Cox) similar to that made by the "Sanitas" Company in Berlin, which had given good results in several hospitals abroad.

Most of his cases had been of the fibrositis-lumbago-sciatica group: several of the fibrositis cases had been sent for X-ray examination of the spine, as prolonged pain had led to a suspicion of spinal disease; all had responded well after only a few treatments. The results in cases of nodular head- and neck-ache had been strikingly successful.

Other cases had been inflammatory, e.g. the case of tracheitis recently reported in the *British Medical Journal* (1934, ii, 822). The tracheal pain had several times been at the onset of a bad feverish cold, but all symptoms had aborted after

two or three treatments. Pain, swelling, and disability following a fractured astragalus had been greatly diminished. A case of otosclerosis, however, had not been improved ; the chief complaint was severe tinnitus, which appeared to have been aggravated after four of the six treatments given. It was possible that otosclerosis was not suitable for this type of diathermy, and he preferred X-ray treatment for that condition.

A final small group was that of cases of painful malignant recurrences, in which a combination of short-wave diathermy and X-ray treatment had been tried. Two were breast-cases and one was gynæcological. One breast-case, with painful bony recurrences in the pelvis and upper end of the femur, had responded particularly well [lantern slides shown]. Following the successful X-ray treatment of a huge inoperable breast-growth (by Coutard's method) pelvic bony metastases were found some months later : early invasion of the right acetabulum and invasion of the left lesser trochanter and shaft of the femur caused much anxiety, owing to the risk of pathological fracture. The patient had been treated by ordinary diathermy elsewhere for supposed fibrositis : so, as she was in ignorance of the condition in the pelvis, a trial was made of short-wave diathermy (8 and 10 metre) together with a prolonged course of X-ray treatment. The skiagrams showed how bony ossification had occurred in all the areas and the patient had been free from symptoms for some time. It was possible that the combined treatment might be a real advance in therapeutics, the pain and disability being more speedily relieved than they would be by X-rays alone, and the diathermy might sensitize the growth to the X-rays.

Dr. Kerr Russell said that he had either given personally, or had supervised 1,792 short- and ultra-short-wave treatments. The term " ultra-short-wave therapy " was now so firmly established that it was unlikely to be superseded.

He had used three different types of apparatus. First, the spark-gap machine known as the " intertherm," then the " radiotherm " valve apparatus, and finally, the " ultra-pandoros " valve apparatus. The intertherm machine was fitted with 22 spark-gaps and it had proved most unsatisfactory and unreliable. The output varied greatly and it was impossible to clean the gaps satisfactorily without dismantling the whole spark-gap system, a process requiring several hours. On the other hand, both valve machines functioned in a most satisfactory and consistent manner and required no attention.

The Schliephake electrodes were the most efficient, but the method of maintaining them in position by rubber bands was unsatisfactory and some form of stand for the exact placing of the electrodes was essential.

He had seen two cases of burns and in each case the cause was apparent. Firstly, if the moisture from sweat was allowed to collect under the electrodes, burning might take place and, consequently when rubber electrodes were used, from one to six layers of felt should always be employed. Secondly, if the cables were allowed to come in contact with the skin, they might cause a burn ; this burning was not noticed at the time. In the one case of this kind which he had seen the epidermis along the area where the cable had lain peeled off some days after the treatment, when the patient was rubbing himself with a rough towel, after a bath.

He thought it was hard to reconcile the remarks of Dr. Turrell and Dr. Eidinow. Dr. Turrell had commented on the absence of a deep-heating effect. Dr. Eidinow had shown the very powerful effect of exposing rats to ultra-short waves. He (Dr. Russell) had seen such excellent results in deep-seated conditions such as osteo-arthritis of the hips and spine, ethmoidal sinusitis, encephalitis lethargica, pneumonia, etc., that the deep effect appeared to him to be obvious.

A number of cases had been treated unsuccessfully with diathermy and had then yielded to ultra-short wave treatment. There seemed to be no doubt that the two treatments were essentially different.

Twelve cases of boils, carbuncles, abscesses, and lymphadenitis had been treated, with excellent results. Eleven cases of sinusitis had yielded in a most satisfactory manner. The relief which ultra-short-wave treatment produced at the beginning of a cold was most striking. Congestion was relieved and breathing through the nostrils became free. It was generally possible to abort a cold if treatment was given at a sufficiently early stage.

Some cases of tinnitus aurium had shown favourable response. Six cases of dental abscess had been relieved. Four cases of prostatitis had been benefited, the patients being able to sleep for several hours without being disturbed, whereas previously they had been wakened every one or two hours throughout the night. In one case of osteomyelitis of several years' duration, a sequestrum was extruded after three weeks of ultra-short-wave treatment, a second thirteen days later, and a third at a further interval of thirty-three days.

A case of septic acne of the face showed a striking improvement after a few treatments. Four cases of asthma showed considerable improvement, and in one case of albuminuric retinitis there was some improvement. Thirty-three cases of osteo-arthritis—chiefly of the hips, knees, and spine—had been treated. In some cases the improvement had been most striking; in others there had been very little relief. In the cases that showed a favourable response, the first improvement noticed was relief of pain, next there was often some increase in movement, but skiagrams taken before and after the course of treatment showed practically no change. Two cases of gonococcal arthritis did extremely well.

The treatment had also proved beneficial for sprains and contusions; a few very striking results had been obtained.

A patient, aged 74, with osteo-arthritis of the left hip-joint of eighteen months' duration, was only able to walk with two sticks at the commencement of the treatment. After the third application, he was able to play three rounds of golf, and there has been no relapse during the five months which have elapsed since the treatment was terminated.

One old man with osteo-arthritis of both hips, who could only hobble a few yards with two sticks, was put on ultra-short-wave treatment of three applications a week. Through a mischance, this patient was not seen by him (the speaker) for some months. He then made the interesting statement that for the first twenty-two treatments there had been no improvement whatsoever in his condition, but that afterwards, at each subsequent treatment there had been a marked improvement, and at the end of 32 applications he was able to walk five or six miles without difficulty. This case showed the necessity for persevering with the treatment for an adequate time.

The pain in a dental abscess case was relieved twenty minutes after the cessation of treatment, which was of fifteen minutes' duration. The swelling, which was of considerable size had subsided considerably after the first treatment and had entirely disappeared after the second application. Skiagrams were taken and it had been possible to save the tooth.

In a case of post-operative pneumonia, thirty minutes' treatment to the affected lung produced a feeling of comfort, the cough became less troublesome, expectoration was less viscid and the temperature fell the same evening to normal, and remained so. Two other treatments were given on subsequent days and the patient made an uneventful recovery.

In concluding he (Dr. Russell) pleaded that interest should be taken in what he considered one of the most important methods of treatment which had yet become available in the whole range of physical medicine. The treatment was just at its

beginning, important developments would inevitably take place, and if the profession neglected this extremely valuable method, it would undoubtedly be exploited by the quack.

Dr. Albert Eidinow (in reply) : The media in which the bactericidal tests were carried out were human blood and human blood-serum ; I selected these as obviously the most natural. Christie and Loomis (*Journal of Experimental Medicine*, 1929, xlix, 305) state that " the biological effects of electromagnetic waves ranging from 15 metres to 1·9 metres in wave-length, or from 8 million to 158 million cycles per second in frequency, can be fully explained on the basis of the heat generated by the induced currents."

I selected wave-lengths of 3·4 and 4·5 metres, as this is within the range which Schliephake and his colleagues claim to be bactericidal, and, clinically, these are the wave-lengths advocated in the treatment of acute and subacute inflammatory lesions.

Section of Therapeutics and Pharmacology

President—J. H. BURN, M.D.

[*December* 11, 1934]

WALTER ERNEST DIXON MEMORIAL LECTURE

Pharmacology and Nerve-endings

By Sir HENRY DALE, C.B.E., M.D., F.R.S.

ABSTRACT.—A brief account is given of the scientific career of Walter Ernest Dixon, and of the importance of his work and his influence for the development of Pharmacology in England. It is suggested that the Memorial Lecture may appropriately deal with some matter of new interest, from one of the fields of research in which Dixon himself was active. Special mention is made of his work with Brodie on the physiology and pharmacology of the bronchioles and the pulmonary blood-vessels, as probably showing the beginning of Dixon's interest in the actions of the alkaloids and organic bases which reproduce the effects of autonomic nerves.

An account is given of Dixon's early interest in the suggestion, first made by Elliott, that autonomic nerves transmit their effects by releasing, at their endings, specific substances, which reproduce their actions; and of his attempt to obtain experimental support for this conception. After the War it was established by the experiments of O. Loewi; and it is now generally recognized that parasympathetic effects are so transmitted by release of acetylcholine, sympathetic effects by that of a substance related to adrenaline.

Very recent evidence indicates that acetylcholine, by virtue of its other ("nicotine-like") action, also acts as transmitter of activity at synapses in autonomic ganglia, and from motor nerve to voluntary muscle.

The terms "cholinergic" and "adrenergic" have been introduced to describe nerve-fibres which transmit their actions by the release at their endings of acetylcholine, and of a substance related to adrenaline, respectively. It is shown that Langley and Anderson's evidence, long available, as to the kinds of peripheral efferent fibres which can replace one another in regeneration, can be summarized by the statement, that cholinergic can replace cholinergic fibres, and that adrenergic can replace adrenergic fibres; but that fibres of different chemical function cannot replace one another. The bearing of this new evidence on conceptions of the mode of action of "neuromimetic" drugs is discussed. The pharmacological problem can now be more clearly defined, and Dixon's participation in further attempts at its solution will be sadly missed.

RÉSUMÉ.—Courte description de la carrière scientifique de Walter Ernest Dixon, de l'importance de son travail, et de son influence sur le développement de la pharmacologie en Angleterre. L'auteur suggère que la conférence dédiée à sa mémoire peut à juste titre traiter de quelque nouvelle matière intéressante dans un des sujets dont Dixon s'occupait. Une mention spéciale est faite de son travail avec Brodie sur la physiologie et la pharmacologie des bronchioles et des vaisseaux pulmonaires, comme étant probablement le point de départ de l'intérêt de Dixon dans l'action des alkaloïdes et des bases organiques qui reproduisent les effets des nerfs autonomes.

L'auteur décrit l'intérêt précoce de Dixon dans l'idée présentée d'abord par Elliott, que les nerfs autonomes produisent leur effet en déchargeant à leurs extrémités des substances spécifiques qui reproduisent leurs effets, ainsi que ses efforts pour obtenir une confirmation expérimentale de cette conception. Après la guerre les expériences de O. Loewi établirent cette idée, et on reconnaît aujourd'hui que les effets parasympathiques sont produits par la décharge d'acétylcholine, et les effets sympathiques par la décharge d'une substance alliée à l'adrénaline.

Des travaux très récents indiquent que l'acétylcholine, par son autre action (" semblable à la nicotine "), agit aussi comme transmetteur de l'activité dans les synapses des ganglions autonomes, et des nerfs moteurs aux muscles volontaires.

Les termes " cholinergique " et " adrénergique " ont été introduits pour décrire respectivement les fibres nerveuses qui transmettent leurs effets par la décharge d'acétylcholine ou d'une substance alliée à l'adrénaline. Il est démontré que l'évidence de Langley et Anderson, existant depuis longtemps, sur les espèces de fibres efférentes périphérales qui peuvent se remplacer dans la régénération, peut être résumée ainsi : Les fibres cholinergiques peuvent être remplacées par des fibres cholinergiques et les fibres adrénergiques par des fibres adrénergiques, mais des fibres de fonction chimique différente ne peuvent pas se remplacer. Les rapports de ces nouvelles connaissances sur notre conception de l'action des médicaments " neuro-mimétiques " sont discutés. Le problème pharmacologique peut être plus clairement défini, et la perte de la collaboration de Dixon dans les efforts futurs pour le résoudre se fera grandement sentir.

ZUSAMMENFASSUNG.—Kurzer Bericht über Walter Ernest Dixons wissenschaftliche Leben und über die Bedeutung seiner Leistungen und seines Einflusses in der Entwicklung der englischen Pharmakologie. Es scheint zweckmässig zu sein dass ein Vortrag zu seinem Andenken von einem neuen interessanten Gegenstand auf dem Gebiet wo Dixon selbst arbeitete handle. Seine Arbeiten mit Brodie über die Physiologie und Pharmakologie der Bronchiolen und Lungengefässe werden besonders besprochen, denn sie zeigen wahrscheinlich den Ausgangspunkt Dixons Interesse über die Wirkungen der Alkaloiden und der organischen Basen welche die Wirkungen der autonomen Nerven wiedergeben.

Dixons frühes Interesse in dem zuerst von Elliott geäusserten Begriff, dass die Wirkung der autonomen Nerven durch die Absonderung an den Nervenenden von spezifischen Stoffen die ihre Wirkung wiedergeben zustandekommt, wird besonders besprochen, ebenso wie seine Versuche experimentellen Beweis dafür zu bringen. Nach dem Krieg wurde diesen Begriff experimentell von O. Loewi bewiesen, und es ist heute allgemein anerkannt dass parasympathische Wirkungen durch Freiwerden von Azetylcholin, und sympathiche Wirkungen durch Freiwerden von einer adrenalinähnlichen Substanz, zustandekommen.

Sehr neue Untersuchungen weisen darauf hin dass Azetylcholin, durch seine zweite (" nikotinähnliche ") Wirkung, auch als Leiter der Wirksamkeit an den Synapsen in den autonomen Ganglien, und vom Motornerven an den willkürlichen Muskel wirkt.

Die Wörter " cholinergisch " und " adrenergisch " sind in die Sprache gekommen um die Nerven zu beschreiben die ihre Wirkung durch Freiwerden von Azetylcholin bzw. von einer adrenalinähnlichen Substanz zu bezeichnen. Es wird gezeigt dass Langley und Andersons Befunde über die Arten von peripheren efferenten Nervenfasen die sich in der Regeneration ersetzen können, die schon lange zugänglich sind, in folgender Weise zusammengefasst werden können : cholinergische Fasern können cholinergische und adrenergische Fasern können adrenergische ersetzen, aber Fasern mit verschiedenen chemischen Wirkungen können sich nicht ersetzen. Die Beziehung dieser neuen Befunden mit unserem Begriff der Wirkungsweise der " neuromimetischen " Mittel wird besprochen. Das pharmakologische Problem kann jetzt genauer bestimmt werden, und die Teilnahme Dixons an den weiteren Versuchen es zu lösen werden wir sehr vermissen.

INTRODUCTORY

THOSE who are responsible for the administration of the Fund which was raised as a Memorial to Walter Ernest Dixon have greatly honoured me by the invitation to deliver this, the first Dixon Memorial Lecture. In later years, I think that my successors will feel that they can best honour Dixon's memory by considering some new and progressive phase of activity in the field of research and teaching which received so strong an impulse from his life and work. It is thus, I believe, that Dixon would himself wish us later to remember him. We should pay but a poor and partial tribute to the memory of any man of science if we were satisfied merely to recall at intervals the state of knowledge during his lifetime in the field where he himself was active, and newly to assess the value of each item of the harvest of discovery which fell to his own reaping. We can better keep his memory alive among those who come after by studying some new and interesting growth from the

ground where he dropped the seed, or, it may be, only prepared the soil for later sowing. So it will be with Dixon; and to-day I shall later ask your attention to some recent experimental data, which throw new light on the meaning of a group of pharmacological actions, which once claimed a central position in Dixon's thoughts and in his research activities.

But on the occasion of this first Memorial Lecture, when the loss of our friend is still fresh in memory, we cannot feel content to pay only such an impersonal tribute to him. The creation of this Memorial signifies much more to those who have raised it than a desire to perpetuate the memory of Dixon's researches, or to provide for the presentation, in the years to come, of new developments in related spheres of investigation. The memory is still vivid with us of Dixon, as a vigorous and inspiring personality, who, more than any other, was responsible for the awakening of interest, here in England, in pharmacology as a progressive science, and as a necessary item in training for the practice of medicine. You will notice that I said England, not Britain, for at the time when Dixon began his work at Cambridge the Scottish medical schools had already their long-established and active departments of pharmacology. In England, on the other hand, pharmacological teaching was limited to a few, often somewhat perfunctory lectures, by one of the physicians in each of the medical schools. At Cambridge, pharmacology did not figure as an obligatory item in the pre-clinical studies. When the Downing Professorship of Medicine fell vacant, Dr. Bradbury, a physician at Addenbrooke's Hospital practising in Cambridge, had been appointed to the Chair, which he held till he died in extreme old age, only a few months before Dixon. But Sir Michael Foster, originator of so much in the Schools of Experimental Medicine and Biology at Cambridge, had seen the need for pharmacology as an experimental science, and it was arranged, when Bradbury became Professor, that an assistant in that subject should be supported from the emoluments of the Downing Chair. It was in this capacity that Dixon came to Cambridge in 1899, and he was still there, as Reader in Pharmacology, at the time of his death, thirty-two years later. Cushny, by some years Dixon's senior, a pupil of Cash at Aberdeen and later of Schmiedeberg, was then away in Ann Arbor, as Professor of Pharmacology in the University of Michigan; and when the creation of a Chair of Pharmacology in University College, London, brought Cushny to England, Dixon had already been six years in Cambridge, and the new stimulus of his activities there had made itself felt far outside his own school. I myself missed the direct contact there, for Dixon came to Cambridge just as I was about to leave; so that whatever piecemeal knowledge of pharmacology may since have come to me has been acquired for special needs, and largely by later friendship with Dixon and Cushny. But from my immediate juniors I soon heard of the new life which had been breathed into pharmacology at Cambridge, where it could be studied, no longer now in terms of traditional *materia medica* and empirical therapeutics, but as a living body of experimental science, closely linked with physiology. Through them I had some share in Dixon's stimulating influence, before I made any personal contact with him, and for some years before I had the great privilege of his close friendship. To the yearly groups of the students who followed them, for more than thirty years, Dixon's lectures and classes continued to give a conception of pharmacology, not as a collection of facts to be learned for examination, but as a lively scientific adventure, in which skill and mental enterprise could hope to win new knowledge, of interest for its own sake, as well as for the part which it might play in building the foundations of rational therapeutics. A number of such students were attracted to obtain a first-hand experience of research in his laboratory; and the results of that experience are in some instances to be measured, not so much by the permanence of the direct contributions to science which resulted from such short-term apprenticeships, as by the lasting effect of an acquaintance with conditions in which observation can be quantitative, and experiment deliberate and controlled.

This attraction which he had for young workers was a part of Dixon's charming and generous personality. His kindliness and his robust humour endeared him to students and colleagues alike. Mrs. Dixon and he made their beautiful old house, in the village of Whittlesford, near Cambridge, a centre of charming hospitality, and a rallying-point for those from many countries who shared his interests. He had real gifts as a raconteur, and his simple and vivid presentation of scientific matter made him an effective popular lecturer, and gave authority to his opinions far beyond the circle of those having expert knowledge of his subject. For a number of years, until his promotion to a Readership at Cambridge with effective control of the department there, Dixon held the additional post of Professor of Pharmacology at King's College, London. This widened the range of his contacts, and brought him into fruitful collaboration with the late W. D. Halliburton and others. On the other hand, apart from the additional teaching obligation, the double duty used much of his time in travelling, and the arrangement probably tended still further to diffuse his already wide interests.

This memorial lecture is not the proper occasion for a systematic review of Dixon's contributions to science. The admirable obituary notice, which Professor Gunn (1932) contributed to the *Journal of Pharmacology and Experimental Therapeutics*, gives a full bibliography of his scientific publications. His earliest papers, on mescal (1899*a*) and *Cannabis indica* (1899*b*), show already his interest in the action of drugs of addiction, to the study of which he returned at intervals throughout his career, and on which he acquired more than a national authority. Nobody who looks at this list of Dixon's publications can fail to be struck by the wide variety of the subjects on which he worked and wrote. He had an almost exuberant interest in any new line of knowledge touching on pharmacology, and a desire to share in its exploration; and his conception of the scope of pharmacology tended to expand well beyond the study of drugs and their action, and to include any procedure finding application in therapeutics. His researches were, accordingly, characterized by range and variety, rather than by intensive and deep exploration in a limited field. It would be presumptuous at this stage to attempt any estimate of the relative permanence and ultimate importance of Dixon's different direct contributions to knowledge. One can already more safely judge of their influence on the work and the ideas of his contemporaries and immediate juniors, and I am inclined to think that this influence was strongest in the cases of his work with Brodie (1903, 1904) on the physiology and pharmacology of the bronchioles and the pulmonary vessels, and his work with Halliburton (1910) on the conditions governing the formation of the cerebrospinal fluid. If I to-day select, from these two, the former for more particular mention, it is because it seems to have provided a starting point for the development of one of Dixon's predominant pharmacological interests.

Bronchioles and Pulmonary Vessels

Brodie and Dixon's (1903) work on the contractility of the bronchioles provided the experimental foundation for a rational conception of the mechanism of asthma. It also, unless I am mistaken, first brought vividly to Dixon's notice the remarkable resemblance between the actions of certain alkaloids and those of autonomic nerves. In this case his attention was, by a curious accident, limited to the resemblance between the effects of vagus stimulation and those of alkaloids like muscarine and pilocarpine, both readily annulled by small doses of atropine. There was waiting for later discovery the equally striking resemblance between the effects of adrenaline and sympathetic nerve stimulation on the bronchioles, both relaxing the tone of the plain muscle which vagus stimulation or muscarine enhanced. Brodie and Dixon seem just to have missed the appropriate conditions for demonstrating this particular sympathetic effect. The remarkable resemblance between the effects of adrenaline

and those of sympathetic nerves must, however, by that date have been in Dixon's mind; for he was working in Cambridge, where this similarity was already a matter of lively interest, through Langley's (1901) researches, and through the remarkable series, then in its initial stages, by which Elliott later (1905) established the general validity of this correspondence, and explored its meaning. In 1903, indeed, Dixon himself published experiments which showed that the actions of adrenaline and those of sympathetic nerves disappeared together, in the rather complex series of paralytic effects produced by the alkaloid apocodeine; and in 1904 his work with Brodie on the pulmonary vessels provided a negative example of the correspondence between the two types of action, the arteries of the lungs, which were not significantly affected by sympathetic stimulation, being shown to be similarly unresponsive to adrenaline (Brodie and Dixon, 1904).

Site of Action of Neuromimetic Drugs

In this paper on the pulmonary vessels Brodie and Dixon included a long discussion of the evidence, including some new items of their own, as to the nature of the reactive structure on which adrenaline produces its effects. Chiefly on the basis of the action of apocodeine, which left the effector cells responsive to other kinds of stimuli when the effects of sympathetic impulses and adrenaline had been simultaneously annulled, they concluded that adrenaline acted on sympathetic nerve-endings. With regard to the direct evidence of Lewandowsky and of Langley, who had both shown that adrenaline retained its full action after the nerves had been cut and allowed to degenerate, Brodie and Dixon were doubtful as to whether degeneration of the nerve-endings, as they used the term, could be assumed, and whether, in any case, a sufficient period had been allowed to elapse, after section, to assure full degeneration. In their own experiments of this kind, the results of which entirely confirmed Langley's, they do not seem to have waited long enough to eliminate this objection to their own satisfaction. Evidence beyond criticism in this respect was given, however, about a year later, by the publications of Elliott and of Anderson. Elliott (1905) completely denervated the pupil by removal of both the superior cervical and the ciliary ganglion, and showed that it was still fully sensitive to adrenaline many months after the operation; while Anderson (1905) obtained corresponding evidence with regard to pilocarpine and the parasympathetic nerve-supply, showing that the reaction of the pupil to pilocarpine had an unlimited persistence after removal of the ciliary ganglion.

Different workers and writers in this field appeared to give somewhat different interpretations to this evidence, though, since there was no difference of opinion as to the available facts, the differences were, perhaps, more verbal than real. It was generally agreed that the impulses in autonomic nerves, and the drugs, such as adrenaline and pilocarpine, which simulated their effects, must act on some structures which completely survived degeneration of the nerves; but that, on the other hand, the annulment of the responses of these structures to nerve impulses or to the mimetic drugs, produced by selectively paralytic alkaloids such as ergotoxine or atropine, left the effector muscle or gland cells still normally responsive to stimuli of other kinds. In view of the evidence from degeneration, the specifically sensitive structures could only be termed "nerve-endings" in a special and doubtfully admissible sense; and though the use of the term has lingered, in pharmacology especially, we shall see that, in the light of the evidence more recently made available, its employment is now even more difficult to justify. Elliott spoke of the structures as "myoneural junctions," and Langley as "receptive substances." Both recognized that they belonged trophically to the effector cells, and the difference in terminology corresponded to relatively small theoretical differences of conception, as to their mode of origin and as to the extent to which they were localized in the

neighbourhood of the true nerve-endings. With his then collaborator, Dr. Fred Ransom, Dixon published in 1912 (Dixon and Ransom, 1912) a systematic and reasoned review of all the evidence concerning this "Selective action of drugs on the peripheral nervous system."

Early Hints of Chemical Transmission

Before these discussions arose Elliott (1904) had already indicated what we can now recognize as the real clue to the meaning of these remarkable similarities, between the actions of certain drugs and those of the two main anatomical divisions of the autonomic nervous system. In a short note published in 1904 he had suggested that the resemblance between the effects of sympathetic nerves and those of adrenaline might mean, that sympathetic impulses, on arriving at the nerve-endings, released small quantities of adrenaline, or of something like it, in immediate relation to the effector cells, which would then give the same responses as to adrenaline artificially applied. Dixon saw that, if this were a true conception, an analogous mechanism would almost certainly be used by parasympathetic nerves, and he pictured the substance transmitting their effects as something like muscarine. Muscarine is a very stable alkaloid, and a knowledge of this fact may well have suggested to Dixon the possibility of obtaining experimental evidence of its release, when the vagus nerve was stimulated. In 1906 and 1907 he published results which seemed to him to give positive support to the conception. In a dog bled as completely as possible, he subjected the vagus nerves to strong and protracted stimulation, removed the heart, boiled it briefly in water, and made an alcoholic extract. This he evaporated to dryness, took up the residue with absolute alcohol to remove salts, and finally brought the soluble portion into saline solution. On applying this solution to the beating heart of a frog, he observed an inhibitor action which atropine removed. With a similar extract from a heart not subjected to vagus stimulation, a similar inhibitor effect was obtained, but a somewhat weaker one. With our present knowledge that the vagus transmitter is not muscarine, but an extremely unstable ester of choline, we can feel no certainty that Dixon had any of it in his extracts. The most recent evidence further suggests that, if he had succeeded in preserving it, the quantity in such artificial extracts from the whole organ would have been no greater with vagus stimulation than without it. Probably the substance responsible for the effects which Dixon observed was free choline. In any case, the experiments were described with so little quantitative detail that they appeared to be of a purely preliminary and tentative nature. From what Professor Gunn tells us, however, Dixon appears to have been discouraged by the scepticism with which the evidence was received. The statement cannot fail to excite the sympathy of anyone who has tried to break new ground in research. If Dixon had felt encouraged, however, to follow the same line of experiment beyond this preliminary stage, we may feel pretty certain that his early evidence would have broken down under his own criticism. What is beyond doubt is that he had already, in 1906, grasped a true conception, with characteristic conviction and enthusiasm. The evidence which really established it, however, came many years later, from a much simpler type of experiment than that which Dixon had tried. Dixon and Ransom's review, published in 1912, and mentioned above, does not consider this explanation of the phenomena there discussed, and we must suppose that Dixon had lost full confidence in it by that date.

At the meeting in 1906 of the British Medical Association in Toronto, at which Dixon made the first mention of his heart-vagus experiments, Reid Hunt with Taveau (1906) described the action of certain esters of choline, and, in particular, the extraordinarily intense activity of acetylcholine, many thousands of times as potent as that of the parent choline. Nobody at the time suspected the possibility

of any thread of connexion between the observations presented in these two entirely independent communications, by pharmacologists from different countries. Seven or eight years later, having come across acetylcholine by accident as a constituent of an ergot extract, and having had experience of the directly physiological interest of other substances which that remarkable drug had brought to our notice, I made a thorough investigation of its actions (Dale, 1914). I was immediately struck by the remarkable fidelity with which it reproduced the effects of stimulating parasympathetic nerves, and with the extraordinary intensity and rapid evanescence of its action, which, I supposed, might be due to its rapid hydrolysis by an esterase —a speculation which later evidence has justified. I made a comparison between the close reproduction of parasympathetic effects by acetylcholine and that of sympathetic effects by adrenaline; both being, for different reasons, highly unstable substances, acting with a brief intensity. I remember very well that, when I first demonstrated some of these effects of acetylcholine to the Physiological Society in January 1914, Dixon came to me and discussed the possibility that this might be his vagus substance. I agreed with him that, if clearer evidence could be produced for the transmission of parasympathetic effects by peripheral release of a chemical agent, acetylcholine appeared to be a more promising candidate for the rôle than muscarine, and one more likely to appear in the animal body. In the event, we had to wait another fifteen years before acetylcholine was found in an animal organ, in such quantity that my colleague, H. W. Dudley, was able to isolate it and identify it chemically (Dale and Dudley, 1929). But one can hardly help wondering whether the new interest excited by its remarkable action might not have encouraged Dixon to renew his attempt to find evidence of a chemical mechanism for the transmission of vagus effects. For him, as for all of us, however, all thought of such academic inquiries was rudely brushed aside by the outbreak of war within less than six months. Dixon spent the following years abroad in the service of the Admiralty, and he never picked up again the thread of what had, for a time, been one of his central scientific interests.

These peripheral effects of acetylcholine, reproducing so closely those of parasympathetic nerves—constituting what I termed its "muscarine action"—were very easily annulled by atropine. Then, with somewhat larger doses, acetylcholine produced another series of effects, due to what I called its "nicotine action," since I traced them to a general stimulation of autonomic ganglion cells (Dale, 1914). Later, other investigators showed that acetylcholine also shared the stimulating effects of nicotine on voluntary muscle, which Langley had described in such detail. At the time, this secondary "nicotine" action seemed rather difficult to reconcile with any suggestion that acetylcholine might be concerned with the transmission of purely peripheral, parasympathetic effects. We shall later consider the significance which recent evidence now enables us to accord to it.

Loewi's Proof of Chemical Transmission

Elliott had made a brilliant suggestion; Dixon had grasped it with characteristic eagerness and enthusiasm, had extended it, and had attempted to verify it experimentally; but we had to wait till 1921 for Otto Loewi, in Graz, to establish, as an experimental fact, the transmission of the effects of autonomic nerve impulses by the peripheral release of specific chemical stimulants (Loewi, 1921). By the simplest imaginable procedure, using the isolated hearts of frogs, Loewi showed that vagus stimulation released into the fluid filling the heart a substance which would transfer the vagus inhibition to another heart; and that when the accelerator action, due to the sympathetic component of the frog's vagus, predominated, an accelerator substance could be similarly detected. When the action of one or the other type of nerve-fibres was paralysed by atropine or ergotoxine, the chemical transmitter of

nervous activity was still released: only its action on the effector cells had been abolished. Loewi and his co-workers were further able to use, to brilliant purpose, the hint, which had not been available to Dixon, as to the kind of substance which the vagus transmitter might be. They showed that it was an unstable choline ester, indistinguishable, in all the properties which a minute scale of experiment allowed them to examine, from acetylcholine. The heart contained an esterase which rapidly destroyed it, and eserine specifically inhibited this esterase, and thereby produced its potentiating action on the effects of the vagus and of other parasympathetic nerves.

Further Evidence

As to Loewi's accelerator substance, the transmitter of sympathetic effects, our further knowledge has come largely from Cannon and his school (Cannon and Bacq, 1931, Cannon and Rosenblueth, 1933). Whether it is adrenaline itself is still open to question. Cannon and his co-workers believe that they have evidence that it is not, and that, in any case, it is capable of appearing in two forms of combination, one producing only the augmentor, the other only the inhibitor effects of sympathetic nerves. They call it "sympathin," to avoid any premature implication as to its chemical nature; though there is already evidence that it is a substance chemically related to adrenaline, even if it is not identical with it. With regard to the parasympathetic transmitter, the evidence which has come, in increasing volume, from the laboratories of many different countries, has given evidence, as was to be expected, of its appearance in connexion with a wide range of parasympathetic effects. This accumulating evidence, moreover, has so strengthened the case for regarding the substance as acetylcholine itself, that there can be hardly any further doubt as to its identity.

The detailed evidence for these two kinds of chemical transmission of autonomic effects has been frequently reviewed. Twice during the present year I have reviewed it myself, dealing on the same occasions with more recent evidence which, rather surprisingly, indicates that a chemical mechanism of this kind also effects the transmission of nervous activity at the synapses in peripheral, autonomic ganglia, and at the motor nerve-endings on voluntary muscle-fibres (*see* Dale, 1934) To-day I must be content with the briefest sketch of chemical transmission in the whole efferent peripheral nervous system, as it now appears in the light of our most recent evidence.

Recent Developments

While in general the distinction holds that peripheral parasympathetic effects are transmitted by the liberation of acetylcholine, and peripheral sympathetic effects by the release of something like adrenaline, this rule is not without exceptions. There are certainly some postganglionic fibres of the true sympathetic system which transmit their effects by means of acetylcholine, as Feldberg and I (1934) have demonstrated in the case of the cat's sweat-glands. Feeling the need of terms to describe nerve-fibres, or their impulses, in terms of a chemical function, which we can no longer regard as corresponding to their anatomical origin, I suggested (1933) the term "cholinergic" to describe those which transmit their action by release of acetylcholine, and "adrenergic" for those which employ a substance resembling adrenaline. The use of such functionally descriptive terms became more necessary when we were led, by stages which I have elsewhere described, to consider whether those actions of acetylcholine, which I classed as its "nicotine" actions, had also a physiological significance. Feldberg and Gaddum (1934), perfusing the superior cervical ganglion with Locke's solution containing a very small proportion of eserine, found that, when the preganglionic nerve was stimulated, but only then, acetylcholine appeared in the venous effluent, in quantity sufficient to enable it to be

identified with practical certainty. Further experiments by Feldberg and Vartiainen (1934) have definitely located at the synapses this liberation of acetylcholine in the ganglion, and have shown that when the ganglion cells are paralysed by nicotine or by excess of eserine, to the stimulus either of drugs such as acetylcholine or of preganglionic impulses, the latter still liberate acetylcholine in undiminished amount, though the ganglion cells can no longer respond to it. There is an obvious and close parallel to the effect of atropine in preventing the action of vagus impulses on the heart, as described by Loewi. I think it is no longer possible to doubt that the liberation of a small quantity of acetylcholine, when a preganglionic impulse arrives at a synapse, plays an essential part in the transmission of the excitation to the autonomic ganglion cell, and that the postganglionic impulse is essentially a separate physiological event; though the correspondence of a single postganglionic impulse to each preganglionic impulse, and the shortness of the delay (not more than 2σ) at the synapse, had given the impression of conduction across the synapse by unbroken propagation. The recognition, however, of acetylcholine as the chemical transmitter at ganglionic synapses, does not mean that its appearance will account for all the phenomena associated with such transmission; and the shortness of the delay at the synapse, leaving no time for diffusion, indicates that the arrival of the preganglionic impulse must liberate a small charge of acetylcholine practically in contact with the ganglion cell, where, having caused the discharge of a postganglionic impulse, it must immediately disappear. Though we may, accordingly, class the preganglionic fibres and their impulses as "cholinergic," the process by which their effects are transmitted to the ganglion cells differs widely in detail from that by which postganglionic parasympathetic impulses use acetylcholine, to produce their modifying actions on the spontaneous activities of plain muscle and gland cells.

The same considerations apply to the evidence suggesting a similar function for acetylcholine, as transmitter of somatic motor nerve impulses to voluntary striated muscle-fibres. The pharmacological affinities between ganglion cells and striated muscle-fibres have often been pointed out. The action of acetylcholine on such fibres again resembles that of nicotine, and is similarly susceptible to paralysis by curare; it is also similarly irregular in its incidence, and conditioned, in the case of most mammalian muscles, by degeneration of the motor fibres. These and other complications have to be borne in mind. On the other hand, the analogies between a ganglionic synapse, and the ending of a motor nerve-fibre on a muscle-end plate, are many. When, therefore, we find, as Feldberg and I (1934) have done, that the effective stimulation, of a purely motor somatic nerve-supply to a perfused voluntary muscle, regularly causes the appearance of acetylcholine in the perfusion fluid, it is difficult to resist the implication, that the liberation of acetylcholine is concerned with transmission of excitation from motor nerve-ending to muscle end plate, as from preganglionic nerve-ending to ganglion cell. These experiments on muscle, begun much later, are far less complete than those on the ganglion; but, so far as they have gone, they have yielded evidence only in favour of such a conception. The difficulties of time relation and repetitive response are the same in the one case as in the other.

Evidence from Regeneration of Nerves

Instead of presenting again the details of such direct evidence, I will ask you to consider the bearing upon it of data, long available, which display the functional similarities and differences between different fibres of the peripheral nervous system, by the method of regeneration after artificial cross-suture of nerves. If we rightly interpret the direct evidence, the preganglionic fibres of the whole autonomic system, the motor fibres to voluntary muscle, and the postganglionic fibres of the para-

sympathetic system can be classed together as cholinergic; only the postganglionic fibres of the true sympathetic system forming a separate class, as being predominantly adrenergic. Look now at the results of the cross-union of nerves, as revealed in a series of papers published by Langley and Anderson between 1897 and 1904. They cut such nerves as the vagus, the cervical sympathetic, the recurrent laryngeal, the hypoglossal, and the fifth cervical. In varying combinations they joined the central cut end of one nerve to the peripheral cut end of another, and awaited the results. And the results showed clearly that the preganglionic fibres of any autonomic nerve, whether sympathetic or parasympathetic, could grow down the degenerating peripheral end of any other preganglionic nerve, and make functional synaptic connexion with the cells of its ganglion, to whichever division of the system it belonged. All preganglionic fibres, therefore, were functionally interchangeable. They showed, further, that any motor fibre to a voluntary muscle could similarly replace any preganglionic autonomic fibre, and make functional synaptic connexion with its ganglion cells; and that, conversely, any preganglionic fibre could replace any motor voluntary fibre, and make effective functional connexion with the corresponding striated muscle-fibres. On the other hand, no replacement could ever be effected of postganglionic sympathetic fibres by preganglionic fibres of either system, or by voluntary motor fibres, and postganglionic sympathetic fibres would make no synapses with ganglion cells or motor endings with voluntary muscle. Any postganglionic sympathetic fibres, however, would replace other fibres of the same type. You will see that, so far, the results seem to fit well with our classification in terms of functional chemistry. They can be simply summarized by stating that any cholinergic fibre will functionally replace any other cholinergic fibre, and that any adrenergic fibre will replace any other adrenergic fibre, but that neither can assume the function of the other.

There remains one case to be considered, and it is one of special interest. The postganglionic fibres of the parasympathetic system are cholinergic, though the conditions under which the acetylcholine, released by the arrival of impulses at their endings, reaches the effector cells, must be widely different from those which obtain at a ganglionic synapse or at a motor nerve-ending in voluntary muscle. The question necessarily arises, then, whether preganglionic or voluntary motor fibres will grow down the track of degenerated postganglionic fibres of the parasympathetic system, and effect any kind of functional replacement of their action on the peripheral effector organ. There is only one case in which the anatomical conditions make it practicable to put this question to the test of operative experiment. The case is that of the ciliary ganglion, and the effects of impulses in the postganglionic fibres, running from it to the sphincter of the pupil, are, of course, peculiarly accessible to observation. The experiments in question were made, and their results recorded in perfect detail, by the late H. K. Anderson, nearly thirty years ago. Anderson (1905) observed that, when the ciliary ganglion was removed from the orbit of a kitten, the sphincter of the pupil perfectly retained its response to pilocarpine, but that the normally potent constrictor effect of eserine disappeared entirely with degeneration of the postganglionic fibres. We may note that Anderson, using the terminology and the conceptions of that time, regarded this as showing that eserine acted on a part of the nerve-ending which degenerated with the fibre, while pilocarpine acted on a more peripheral portion of the neuromuscular mechanism, which survived. To-day I think we can more reasonably attribute the effect of eserine to the accumulation of acetylcholine, the liberation of which, by the play of impulses in postganglionic fibres, is normally balanced by the destructive action of the cholinesterase, which eserine inhibits. When the nerve-fibres are gone, no acetylcholine is liberated, and eserine no longer acts. The point of special interest for our present purpose, however, is that Anderson found that the action of eserine returned, if the animal was kept for some months after operation, and that

the pupil then, under partial eserine action, recovered its response to illumination of the eye. Regeneration appeared to have taken place. The fact puzzled Anderson, as being in apparent conflict with Langley's evidence, obtained from true sympathetic nerves, that postganglionic could never be replaced by preganglionic fibres. He tested the possibility further, however, by a second operation, in which he cut the scar tissue which had formed between the preganglionic stump and the former postganglionic bundle; with the result that the action of eserine again disappeared. In one experiment Anderson was able to trace the origin of the fibres which had grown across the gap and had made at least a partially functional connexion with the pupil, and he found that they came not only from the preganglionic stump, but from motor branches of the oculomotor nerve to extrinsic ocular muscles, which had been inevitably injured at operation. The functional union with the sphincter was not quite normal, since artificial stimulation of the oculomotor trunk had little effect; but it was sufficient to puzzle Anderson, who honestly recorded his beautiful observations, and confessed himself unable to explain them. To-day I think we may look on them as providing the missing item of evidence required to justify the general statement that any cholinergic fibre can functionally replace any other. Alternatively, we might regard them as affording independent, confirmatory evidence of the cholinergic function of preganglionic and voluntary motor fibres.

The Case of Sensory Fibres

If we attribute such evidential value to the results of positive regeneration experiments, we cannot properly ignore the significance of others which were negative in result. We thought, at one time, that the vasodilator peripheral axon branches from sensory fibres were cholinergic (Dale and Gaddum, 1930), but the most recent observations of Hinsey and Cutting (1933) seem to have disposed of the evidence on which that view was based. Dikshit (1934), on indirect evidence, has suggested that sensory impulses in fibres of the vagus produce their effects at central synapses by liberation of acetylcholine. Some experiments, by Feldberg and Schriever, in my own laboratory, have given direct evidence, indeed, of the appearance of acetylcholine in the cerebrospinal fluid when the vagi are centrally stimulated; but our knowledge of the factors involved in this phenomenon is not yet complete enough to warrant an interpretation of its meaning. Langley and Anderson, we must note, were unable to obtain any functional replacement of preganglionic or voluntary motor nerve-fibres by sensory fibres, whether these were growing peripherally or centrally from a sensory ganglion; so that regeneration experiments give no support to the suggestion of a cholinergic function of sensory fibres, either in the case of their peripheral, vasodilator axon-branches, or in that of their endings in central synapses. On the other hand, the antidromic vasodilatation so closely resembles that produced by autonomic nerves, and central synapses have so many points of analogy with those in autonomic ganglia, that it is reasonable to expect that some definite evidence of chemical transmission may yet be found in these cases also. Other specific chemical transmitters of nervous action, in addition to the two already known, may yet await discovery. It is to be noted, further, that in the cases for which direct evidence is already available, the phenomena of regeneration appear to indicate that the nature of the chemical function, whether cholinergic or adrenergic, is characteristic for each particular neurone, and unchangeable. When we are dealing with two different endings of the same sensory neurone, the one peripheral and concerned with vasodilatation and the other at a central synapse, can we suppose that the discovery and identification of a chemical transmitter of axon-reflex vasodilatation would furnish a hint as to the nature of the transmission process at a central synapse? The possibility has at least some value as a stimulus to further experiment.

A Change in Pharmacological Conceptions

The general conception of the mode of transmission of the effects of nerve impulses, which is even now taking shape, will obviously entail some revision of pharmacological conceptions and terminology. It no longer has any scientific meaning to say that acetylcholine and adrenaline reproduce the effects of parasympathetic and true sympathetic nerves, because they act on the respective types of "nerve-endings." It is truer to say that parasympathetic nerve impulses reproduce the peripheral effects of acetylcholine, because, when they arrive at the nerve-endings, they liberate that substance in relation to the effector cells; and the same is true of sympathetic nerve impulses and adrenaline, with the still necessary reservation as to the chemical identity of the transmitter. In either case the action of the chemical substance must be on the effector cells, and not on the nerve-endings. When atropine or ergotoxine produces its specific paralysis, it does so by rendering the effector cell specifically insensitive to acetylcholine or to adrenaline. Similar conceptions, *mutatis mutandis*, apply to the actions of acetylcholine on ganglion cells and striated muscle-fibres, and to the annulment of these actions, with blockage of the corresponding nervous excitations, by nicotine and curare respectively. We still have to account for the fact that, when a substance like acetylcholine is artificially applied, the effector cells responding to its action are predominantly those in relation to which it is normally liberated as the transmitter of nerve impulses. The correspondence, in this case, cannot be regarded as exact; acetylcholine causes, for example, arterial dilatation widely outside the limits of any cholinergic nerve supply yet demonstrated. It is close enough to have an important significance, but its meaning is by no means clear. We must remember that the effector cells having a parasympathetic innervation, and accordingly habituated to responding physiologically to acetylcholine, also show a highly selective response to other substances, such as pilocarpine and arecoline, which have no recognizable similarity, in chemical structure or properties, to acetylcholine. It is similarly difficult to trace more than a general chemical similarity between adrenaline and some of the substances which share, to varying degrees, its selective action. I doubt whether the use of such terms as "myoneural junctions," or "receptive substances," to describe hypothetical components of the effector cells, to which their selective responses may be attributed, will serve any longer to clarify the issue. Elliott's term "myoneural junctions" was introduced with reference to involuntary muscle cells and their autonomic innervation, but there is no evidence in this case for a localization of the specific excitability in the neighbourhood of the actual nerve-endings, such as the term might imply. Langley's term "receptive substances" may be used so as to imply nothing more than the existence of the specific excitability, which it is supposed to explain, but as Langley himself used it, it connotes a chemical fixation of the stimulating substances, for which there is no evidence, and with which, indeed, the lack of chemical similarity between substances having a closely similar action is hardly compatible. In the special case of the voluntary muscle-fibre, the receptive or excitable structure may be histologically distinguishable from the contractile elements, and localized near the nerve-ending as the end-plate; and it is interesting that Langley, in seeking evidence for an unlocalized "receptive substance," should have chosen voluntary muscle for his experiments with nicotine, so that he was obliged to describe a preëminence of sensibility to that substance in the neighbourhood of the nerve-endings. We cannot generalize, however, from such a highly specialized and complex structure as that of the voluntary muscle-fibre, and I do not think that, in most cases, we are entitled to draw or to imply any more exact conclusion than that the action of the specific transmitters, and of other similarly active bases, is on the effector cells and not on the nerve-endings.

How does the nerve impulse, on reaching the nerve-ending, cause the chemical transmitter of its action to appear? The evidence is meagre as yet, and not wholly

consistent. The latest results (Vartiainen, 1934) support the view that the transmitter is not newly formed by synthesis as each impulse arrives, but held in some inactivating and protective complex, from which the nerve impulse releases it, and from which it is easily separated by ordinary methods of chemical extraction. Experiments by Engelhart (1931) show that, in the one case yet investigated, this depot is dependent for its maintenance on the integrity of the nerve-endings, and that it disappears or becomes depleted when the nerve-fibres degenerate. (We may note, in passing, the probability that the exaggerated sensitiveness of the denervated effector cells, to the artificial application of the chemical transmitter, may be conditioned by this disappearance of its depot and failure of its normal release.) In accordance with the interpretations given to earlier evidence, we should take this disappearance to mean that the depot belongs to the nerve-ending; but it may merely mean that its maintenance is dependent on the arrival of nerve impulses at a normal rate, and that its depletion with nerve degeneration is comparable to an atrophy of disuse. The permanent association, however, of a particular neurone with one kind of transmission would be more easily interpreted, if the transmitting mechanism were actually a part of the nerve-ending. On either conception it seems possible to give a clearer interpretation to the actions of the only two specifically stimulant bases, for which an action on nerve-endings appears to be really supported by evidence. One case, that of eserine, I have already discussed in describing Anderson's observations. The other is that of tyramine, certain sympathomimetic actions of which were found by Burn and Tainter (1931) to disappear with nerve-degeneration and under the action of cocaine. The fact that its vasoconstrictor action was found by Burn (1930) also to disappear during artificial perfusion, and to be restored when adrenaline was added to the perfusing blood, suggests that tyramine may act by liberating the transmitter from the depot, cease to act when this is depleted, and act again when it is replenished. The same may be true of the sympathomimetic effects of ephedrine, which is chemically not distant from tyramine, and loses its action in the cat similarly with nerve-degeneration (Pak and Tang, 1933). In no other instances known to me, and in no other sense, does the description of a specific effect as due to action on nerve-endings seem yet to be justified by the evidence now available.

To the fundamental pharmacological problem, why a particular type of chemical structure, or, more mysteriously, several apparently unrelated types, should be associated with a specific action on particular types of reactive cell, we have made no nearer approach. The newer evidence merely exposes the nature of the problem, and clears the ground for an eventual attack upon it. I can picture the eager interest with which Dixon would have welcomed this clarification, which he, indeed, had in part foreseen. As pharmacology approaches one of its fundamental tasks, it will sadly miss his exuberant fertility in ideas, and the stimulus of his buoyant optimism.

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Clinical Section

President—E. G. SLESINGER, O.B.E., M.S.

[*November* 9, 1934]

Two Cases illustrating Dilatation of the Aorta.—TERENCE EAST, M.D.

I.—Carpenter, aged 59. First seen three years ago, with a history of pain across the chest for a year. Examination shows slight loss of resonance on percussion over the upper part of the sternum. Most noticeable is the loud booming aortic second sound, which can be heard as far as the back, between the left scapula and the spine. The air entering into the left upper lobe behind is impaired.

A skiagram shows dilatation of the arch of the aorta, amounting to an aneurysm at the upper part of the descending portion.

Wassermann reaction positive.

No advance in the condition since coming under observation. Treated with iodide and mercury.

II.—Coal carrier, aged 71. First seen two and a half years ago, with pain in chest, cough, and dyspnœa. There is a hollow booming, widely transmitted, aortic second sound. Episternal pulsation. Slight enlargement of left ventricle. Blood-pressure 150/100. Skiagram shows dilatation of the aorta.

Wassermann reaction negative.

This case shows dynamic dilatation of the aorta, due to hypertension and arterial degeneration.

The two cases illustrate the importance of changes in the aortic second sound in the diagnosis of disease in the aorta.

Dr. EAST said that there were two important types of alteration in sound from the normal. One was associated with high blood-pressure, when the aortic second sound took on a musical twanging character, the *bruit de tabourka*, and became much louder than normal.

In the other there was an increase in the loudness of the sound, but it took on a hollow booming low-pitched note, and this sound was usually conducted well up the sternum. The cause of this change was dilatation of the aorta, most likely due to syphilis. This type of change was especially significant when associated with a normal blood-pressure. There was not necessarily aortic incompetence. A systolic murmur might be present with either kind of alteration.

Congenital Malformation of the Heart. Complete Dextrocardia. Pulmonary Stenosis (Conus).—PHILIP ELLMAN, M.D.

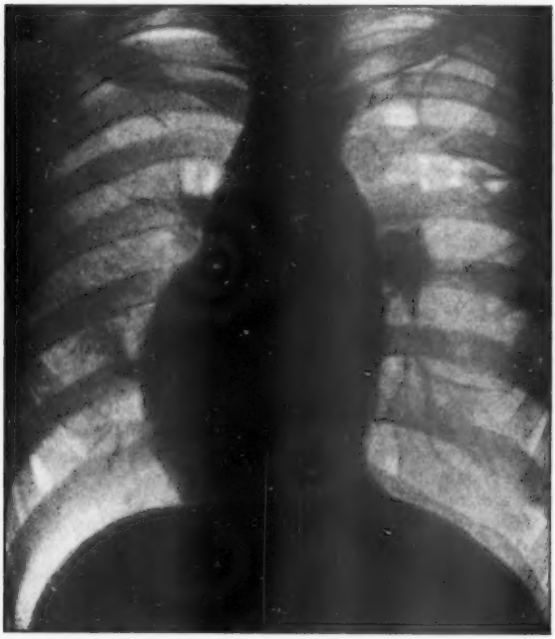
F. W. L., male, aged 21, a dental mechanic, gives a history of periodic attacks of hæmoptysis (the first having been in October 1933) amounting in one instance up to one pint, for which he had treatment in sanatoria from December 1933 to October 1934. He is now feeling quite fit, except for slight breathlessness on exertion, and palpitation.

Previous history.—Shortness of breath when an infant. No history of rheumatism or scarlet fever.

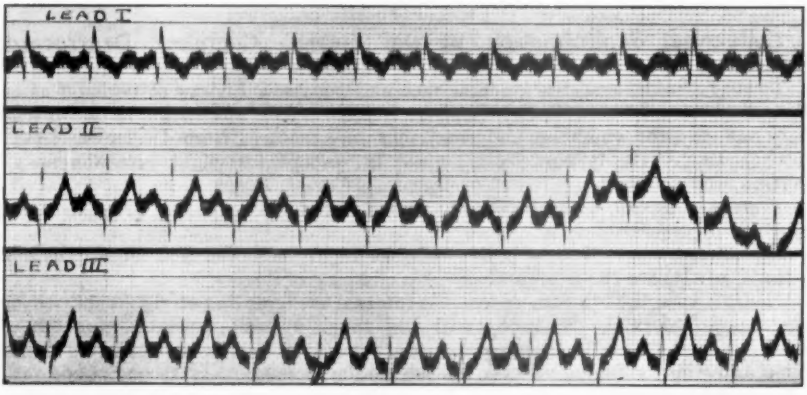
On examination.—Normal build. Cheeks highly coloured and slightly cyanotic in tinge, as also are the conjunctivæ. No clubbing of fingers.

Heart: Apex beat in fifth space, just internal to nipple line on right side; rhythm regular; rate normal. Systolic thrill and rough systolic murmur, best felt and heard in the second right intercostal space, but almost completely replacing the first sound and well conducted all over the præcordium; pulmonary second sound rather accentuated. Blood-pressure, 130/75.

Electrocardiographic examination: Typical complete inversion of lead I, characteristic of dextrocardia, with apparent transposition of leads II and III.



Congenital dextrocardia with pulmonary stenosis. Note the prominence in the region corresponding to the pulmonary conus (right side in this case) and the infiltration in the upper zone of the left lung.



Electrocardiogram of case of congenital dextrocardia with complete situs inversus. Note the inversion of all waves in Lead I. Leads II and III are reversed.

X-ray examination of heart: Complete dextrocardia. Definite prominence in region corresponding to the pulmonary conus. The stomach (skiagram with bismuth meal) is on the right side and the liver is on the left.

Lungs: Some impairment, prolonged expiratory breath sounds, and post-tussive crepitations in left upper zone; X-ray examination shows annular shadow with infiltration in this zone; the lesion is not, however, active.

The condition is one of dextrocardia with complete "situs inversus" which is normally, in itself, of no great clinical significance. It is unusual, however, according to Rösler and others, to find associated congenital cardiac defects. In this particular case there is a definite congenital cardiac lesion, most likely a pulmonary or conus stenosis. Dr. Evan Bedford kindly saw this case with me at the National Hospital for Diseases of the Heart. It is of interest that Fishberg has noted, in a few instances, the association of dextrocardia and pulmonary tuberculosis.

Dr. W. M. FELDMAN referred to two cases of his own of complete transposition of viscera. One of these, in a baby a few weeks old, he had published in the *British Journal of Children's Diseases*, 1925, xxii, 136. The electrocardiogram showed all the waves inverted except the T wave, and this was taken as evidence of myocardial degeneration. The baby died, but no post-mortem examination was allowed. The second case was in a girl, aged about 8 years, who complained of pain simulating appendicitis, but who, on laparotomy, was found to have a maldeveloped cæcum with no appendix.

Cushing's Pituitary Basophilism (Cushing's Disease).—PHILIP ELLMAN, M.D.

B. L. S., female, single, aged 26, typist, previously healthy, gives a history of complete cessation of hitherto regular and normal menses, in September 1933. Her weight then began to increase (from 8 st. 3 lb. to 9 st. 3 lb. within a short period) and she began to have severe headaches. Her face became fat and florid, and her lower eyelids and feet began to swell. Whilst the hair of her scalp began to grow thin and to fall out, she was surprised to observe the definite growth of fine short hair on the sides of the face and around the lips. The deposition of fat was confined primarily to the regions of the chest, face, and back of the neck, and was somewhat painful. There was no adiposity of the extremities. She further complains of lack of energy, and of bruising readily, and she has noticed recently that her nails have become extremely brittle.

Family history.—Father always healthy (killed during the Great War); mother healthy; one brother, healthy.

Previous history.—Measles, whooping-cough, and chicken-pox in childhood; tonsillitis in 1933. Otherwise quite well. Her menses began at the age of 14. Her doctor has been giving her thyroid for some months, and her weight is now 8 st. 7 lb.

Condition on examination.—Face round, plump, and plethoric. Fine short hair around the lips, and on the face and the spine, but no abnormal deposition of hair in other areas. Not undersized; no kyphosis. Skin rough and dry; purplish striæ on legs and on lower quadrants of the breasts. Very slight contusion provokes ecchymoses.

Central nervous system: No abnormal findings. Pupils equal; react to light and accommodation. Discs normal.

Cardiovascular system: Heart not enlarged; rhythm regular; no murmurs. Blood-pressure: systolic 170/190, diastolic 100/110. A radiocardiogram shows the heart to be normal, in shape, size, and position.

Gynæcological examination (Mr. Martin Oldershaw): Uterus small, otherwise normal pelvis.

No clinical evidence of disease in any other system.

Pathological investigations (Dr. Haler).—Urine: Specific gravity 1013; reaction alkaline; no albumin; no casts—phosphatic débris only; sterile on culture. Urinary

urea 1·4%. Blood urea 28·5%. Blood-count: Total red cells 6,810,000 per c.mm.; C.I. 0·98; total white cell count 10,312.

Skiagram of skull and spine (Dr. Vilvandré): No obvious skull lesion. Bone not very dense generally. Suggests some decalcification. Normal pituitary fossa.

My attention was first drawn to this case as one of vascular hypertension which has proved not to be cardio-renal in origin. The outstanding features are:—(1) Rapidly acquired obesity confined principally to the face and chest (the limbs are quite normal). (2) Sexual dystrophy, shown by early amenorrhœa and a small uterus. (3) Alteration in normal hirsuties, shown by tendency to hypertrichosis of face. (4) Vascular hypertension. (5) Dusky, plethoric appearance of skin, with purplish striæ and ecchymoses. (6) Erythræmia. (7) Excessive fatigue. (8) Tendency to osteoporosis.

Discussion.—Dr. PHILIP ELLMAN said that Dr. Parkes Weber had reported very accurately and fully one of the early cases of what proved at autopsy to be this condition of "Cushing's disease."[1] His description had since become a classic. Dr. Weber then thought that the main features of his case could not be explained by the small adenoma of the pituitary found at post-mortem examination, but in recent years the influence of the pituitary body—as Cushing had pointed out—on the development and regulation of the genital system had been realized. There was no evidence of macro- or microscopic abnormality in the adrenal glands in Dr. Weber's case, but the possibility of a hypersecretory influence of the adrenal cortex, even in the absence of microscopic changes, was a very real one. This case had come to his (the speaker's) notice as one of vascular hypertension in a young girl, which proved on investigation to be due to pituitary disease.

Dr. F. PARKES WEBER regarded the case as one presenting all the known signs of what he preferred to call Cushing's pituitary syndrome, though the patient was in relatively fair health. In addition to the signs enumerated by Dr. Ellman he would specially draw attention to the commencing change in texture of the skin in front of the legs, which he thought was not merely a part of the tendency to a kind of dusky cyanosis, though connected with it. Dr. Weber thought that it was not yet quite proved that the minute basophilic adenoma found in the anterior lobe of the pituitary in these cases was the primary cause of the syndrome.

Postscript.—Since this case was shown, the patient has received four treatments by deep X-ray therapy to the skull, by Dr. Vilvandré. Following the last treatment she has had, for the first time in over twelve months, a practically normal menstrual period. [P. E.].

Childhood Obesity with Multiple Congenital Abnormalities: Case for Diagnosis.—ERNEST FLETCHER, M.B.

M. V., female, aged 9.

Under weight at birth; backward; walked at age of 3, and talked at age of 7, but only in single words, not in complete sentences. Shy, afraid of strangers; "mothers" other children.

Past history.—Said to have had rickets at age of 6 months.

Condition on examination.—A fat child; face blue; head small in proportion to body. Only says a word now and then. No bossing of skull. Bridge of nose depressed. Eyebrows sparse. Inner canthus of eye higher than outer canthus. Pads of fat under nipples and over pubis. Trace of pubic hair. No striæ atrophicæ. Fundi could not be seen satisfactorily; visual fields apparently normal. Hands fat and trident-shaped; small fifth digit on right hand; phalangeal joints fusiform. Extremities blue and cold. Tongue natural.

Heart: Systolic bruit at pulmonary base, diminishing towards apex. Second pulmonary sound accentuated. Blood-pressure 110/70.

Radiological examination: Congenital malformation of fifth metacarpal bone of right hand. Secondary centre of ossification for head of this bone is missing, also epiphysis for terminal phalanx. Pituitary fossa long in proportion to rest of skull. No abnormality of sutures.

[1] *Brit. Journ. Derm. and Syph.*, 1926, xxxviii, 1.

Carbohydrate tolerance: Fasting sugar 0·085%. The curve rises to 0·154% at one hour, and falls to 0·09% at two hours.

Wassermann reaction negative.

Basal metabolic rate: −9%, calculated for present weight, which is 35 kilos.

Discussion.—Dr. PARKES WEBER regarded the case as one of multiple congenital abnormalities: (1) The bony defect in one little finger; (2) the important congenital cardiac malformation; (3) an abnormality in cranial development, shown by the peculiar face—not definite hypertelorism—and by the apparent flattening out of the pituitary fossa; (4) the suggestion of slightly Mongoloid eyes; (5) an inborn error of metabolism giving rise to the obesity, which might possibly be connected partly with congenital thyroidal insufficiency.

Dr. PEARSE WILLIAMS said that there were certain features in this case suggestive of Mongolian imbecility. The coarse skin and flush of the cheeks, slanting eyes and the shape of the hands. He had also found on inquiry that the child was fond of musical sounds. He considered that the obesity was probably a separate factor from the mental defect, and although it was his own practice to give thyroid or a combination of thyroid, thymus and pituitary in similar cases, and he would suggest trying it in this case, he did not think that it would have any very beneficial effect.

Enormous Goitre in a Deaf-Mute.—N. L. ECKHOFF, M.S.

History.—Family history irrelevant. Deaf and dumb since birth. Intelligence normal. No previous illnesses.

Swelling in neck first noticed four years ago. Right side enlarged first, shortly followed by left side. Steady increase in size since. No pain, but discomfort and breathlessness.

On examination.—Marked enlargement of whole thyroid gland, with some downward projection on right. The gland is soft and fairly smooth. No murmur. Breath sounds harsh. Dilated veins over gland. No exophthalmos or tremor. No clinical abnormality of cardiovascular system. Resting pulse 90.

Investigations.—Considerable compression of trachea seen in skiagram. Electrocardiogram normal. Serum calcium, 7·9 mgm. (normal 10). Electrical threshold stimulus, 2·1 ma.

Stricture of a Bronchus.—A. WILLCOX, L.R.C.P., M.R.C.S. (introduced by Dr. J. LIVINGSTONE).

Patient is a man aged 35.

Past history.—May 1933, pleurisy in left side. Skiagram showed some shadowing in left upper zone. Right lung clear. Notified as suffering from pulmonary tuberculosis.

History of present condition.—Admitted to Brompton Hospital under Dr. Livingstone, August 20, 1934. Complained of marked dyspnœa on exertion since June 1934, tight feeling in chest and dry cough. Felt very well generally. Did not think he was losing weight.

Condition on examination.—Appeared to be well nourished. Diminished movement of left side of chest, impaired percussion note on this side and very weak air entry.

A diagnosis of blocked left main bronchus was made. This was confirmed by a skiagram of the chest after injection of lipiodol. The skiagram also showed an enlarged calcified gland near the site of obstruction.

The Wassermann reaction was negative.

August 28, 1934: Patient was examined bronchoscopically by Mr. J. E. H. Roberts. The left bronchus was found to be narrowed to an oblique slit one inch from its commencement. The mucosa was œdematous and thickened. Bougies, in size from No. 3 to 22, were passed through the stricture with some difficulty. Two ounces of

pus were aspirated from beyond the stricture and a section was taken from the wall at the constricted area for microscopical examination. *Report*: Evidence of chronic inflammation. The pus grew *Staphylococcus aureus*. The sputum has been free from tubercle bacilli throughout.

It was concluded that the obstruction of the bronchus was due to fibrosis occurring around the gland seen at this site.

Since the initial bronchoscopy the patient has been bronchoscoped and dilatation performed at weekly intervals. Clinically the stricture appears to remain patent for about three days, but after that the air-entry at the left base disappears. When the stricture is patent, coarse consonating crepitations are present at the left base and bronchiectasis is apparently forming behind the stricture. There is no change in the general condition of the patient.

Dr. ERNEST FLETCHER said that the calcified gland shown on the skiagram did not apparently abut on to the bronchus, but was separated from it by an appreciable interval.

Further, it was calcified and therefore healed, so that it would be unlikely to account for what was apparently a progressive lesion.

In view of the development of bronchiectasis in this lobe, the natural course of the case must be downhill. If repeated bronchoscopy had failed to reveal the cause of the bronchial obstruction, the only effective line of treatment seemed to be lobectomy.

Postscript.—Ten days after the meeting, bronchoscopy was performed again, and a second piece of tissue was removed from the stricture, for microscopical examination. This showed a columnar-celled carcinoma, and therefore Mr. Roberts inserted radon. [A. W.].

Axillary Metastases from Epithelioma of Finger, treated with Radon.—W. MCN. NIBLOCK, F.R.C.S. (for HAROLD EDWARDS, F.R.C.S.).

John H., aged 75, has metastases in the right axillary glands, from carcinoma of the right index finger, which was amputated four years ago.

Radon seeds were inserted into the glands on September 7, 1934.

Mr. N. ECKHOFF said he did not think the axillary region should be attacked with the knife. His own experience of epithelioma of the skin had been depressing. In most cases recurrence along the lymphatic tract took place, especially if the removal of the primary tumour had not been sufficiently wide. In this case, the primary operation had been a good one, nevertheless, recurrence had taken place, and he thought it was doubtful that all infected tissue could be completely excised.

Trophic Arthropathy of Charcot Type in the Left Elbow, with Rupture of the Biceps.—H. S. STANNUS, M.D.

E. H., female, aged 58, weight 167 lb., a widow since 1924; sixteen children, aged from 40 to 14 years (all alive and well, according to mother); no miscarriages. Admitted to the French Hospital, October 3, 1934, under Mr. Burns, with what appeared to be a rupture of the left biceps. She had wakened on the morning of the day of admission to find an enormous swelling to the inner and anterior aspect of the left upper arm; the swelling was painless and not tender. There was no history of trauma.

At operation the following day the sheath of the biceps was found to be ruptured, and partly within the sheath and partly outside there was a very large hæmatoma. The blood-clot was removed and the muscle and sheath were repaired, with good result. A week later patient complained of occipital headache. The blood-pressure was 180/75, but a fortnight later it was 130/85, and there was less headache. The patient then came under my care. Routine clinical examination had revealed an arthritis of two or three years' duration in the left elbow, which, on radiological examination, was seen to have the typical characters of a Charcot's joint.

Apart from bilateral myosis, rather increased knee-jerks, indeterminate plantar responses and absence of tendon reflexes in the affected arm, there are no abnormal clinical findings in the nervous system. Urinalysis normal. Blood examination normal. Wassermann reaction: In blood-serum, completely negative; in cerebrospinal fluid negative. Further examination of the cerebrospinal fluid showed two lymphocytes per c.c.; total protein 30 mgm. %; sugar not increased; globulin, negative.

The case is one in which tabes may probably be excluded and syringomyelia must be considered.

Osteochondritis Dissecans.—T. T. STAMM, F.R.C.S. (introduced by the PRESIDENT).

History.—C. M., male, aged 19, four years ago was struck by a hockey-stick on the left patella while the knee was flexed. The injury caused little trouble at the time, but shortly afterwards he went on a walking-tour, when he found that he suffered discomfort unless he kept the knee straight and walked with a straight leg. This lasted for a fortnight, after which the knee improved and, except for occasional slight pains, remained well for two years. During the last two years the pain has gradually returned, and the patient has again had to keep a straight leg for comfort in walking. There has never been any locking of the joint.

A week ago the knee swelled and became more painful. The patient found that walking with the knee straight was now painful, and he was obliged to walk with it slightly flexed. He also noticed that on several occasions when flexing the knee he felt something click inside the joint which became locked for the moment.

Physical signs.—Left knee: Extension full, flexion slightly limited, some fluid in joint. Some tenderness over articular surface of internal condyle when examined with the knee flexed.

Radiological examination shows osteochondritis dissecans of the internal condyle.

Erythro-leukæmia (Leukæmia following Long-standing Erythræmia—Polycythæmia Vera, Vaquez's Disease).—E. STOLKIND, M.D.[1]

The patient, a man aged 60, has been under my observation continuously since 1921 at the West End Hospital for Nervous Diseases.[2] He has suffered from erythræmia (Vaquez's disease, polycythæmia vera) since about 1918, has since then been unable to follow his occupation, and was at that time advised by a doctor to have all his teeth extracted as a treatment for his disease; the teeth were in good condition. The advice was followed without any good result. He never used artificial teeth, and did not suffer from gastro intestinal disease.

During the last thirteen years, the spleen and liver have gradually increased in size. The first blood-counts showed R.B.C. 7,000,000 to 10,000,000 per c.mm.; Hb. 140% to 160%; W.B.C. 16,400 to 20,400. Venesection, which is rather a stimulus for new blood formation, and potassium iodide gave slight subjective improvement for a few weeks only, and there was no improvement at all after treatment with benzol.

In 1922 Dr. J. H. Douglas Webster gave him eleven full applications of X-rays to the sternum, thighs, legs and arms, with considerable subjective improvement which lasted for about ten months. Blood-count, 1924: R.B.C. 9,350,000; Hb. 134%; W.B.C. 13,800. In 1925 Dr. Douglas Webster gave eight further full applications of intensive X-ray to the thighs, legs and arms with a considerable improvement of the subjective symptoms. In 1926 the nervous symptoms returned;

[1] Patient was shown at the Clinical Section by Dr. E. Stolkind, *Proc. Roy. Soc. Med.*, 1922, xvi, 35 (Clin. Sect.); 1926, xix, 19; 1931, xxiv, 925.

[2] In the beginning of 1921 he was seen by Dr. Parkes Weber, "Polycythæmia," etc., 1921, p. 86.

the legs became periodically œdematous. There were tar stools occasionally. Sodium citrate gave no result. In 1927 Dr. Douglas Webster gave a third series of eleven X-ray applications. Since then the blood-count has ranged between R.B.C. 6,230,000 and 7,140,000; W.B.C. 5,200 and 14,000; Hb. 106% to 112% (Dr. Carnegie Dickson); B.P., 140 to 160, systolic, and 90 to 120 diastolic. The spleen and liver were two fingerbreadths below the costal margin.

At the end of 1930 phenylhydrazine hydrochloride—a good, but dangerous, drug which may have a cumulative action—was given (53 gr. in twenty days) and marked anæmia (hæmolysis) and thrombosis of saphenous vein followed; this effect has been observed in three other yet unpublished cases. The liver increased in size and reached to the level of the umbilicus. Later the R.B.C. reached 6 to 7 million, but the liver remained enlarged.

For the last few years, and especially during last year, the patient has gradually become weaker, and the spleen and liver have become more enlarged. In January 1934, the spleen reached the umbilicus line; the liver was two fingerbreadths below this line; later they increased still further. Spleen was one fingerbreadth below umbilicus. R.B.C. gradually diminished in number while W.B.C. increased. In April 1934, R.B.C. numbered 3,280,000; W.B.C. 72,800; Hb. 71%; myelocytes 22,000. The number of W.B.C. continued to increase; for instance, in June there were R.B.C. 3,000,000; W.B.C. 300,000; Hb. 60%; myeloblasts 3%; myelocytes 10%; metamyelocytes 19%; polys. 52%; eosinos. 2%; basos. 2%; monos. 6%; lymphos. 6%. After X-ray treatment (given by Dr. Carter Braine), W.B.C. 16,000; the spleen diminished in size and was only palpable by respiration. The number of W.B.C. is at present gradually increasing. The patient is very weak and gradually sinking.

BLOOD-COUNT.—1934.

	April 18	June 27	July 12	July 25	August 14	Sept. 4	Sept. 26
Red blood-cells	3,280,000	3,000,000	3,300,000	2,300,000	2,600,000	3,200,000	3,400,000
Hæmoglobin	71%	60%	66%	46%	45%	57%	62%
Colour-index	1·1	1	1	1	0·85	0·9	0·91
White blood-cells	72,800	300,000	180,000	16,000 (!)	18,400	50,000	37,000
Polymorphonuclears ...	53%	52%	67%	77%	75%	68%	76%
Lymphocytes	7%	6%	5%	8%	12%	5·25%	9%
Eosinophils	1%	2%		8%		2·75%	3·5%
Basophils		2%		1%		0·75%	1%
Myeloblasts	4%	3%					
Myelocytes	31%	10%	4%		No true myelocytes	1·75%	
Metamyelocytes		19%	24%	3%	13%		1·5%
Cells intermediate between metamyelocytes and polymorphonuclears						21·5%	5%
Monocytes		6%		3%			4%
Normoblasts	4%	+				Few	
Polychromasia		+		+	+	++	
Punctate basophils ...		+			+		
Anisocytosis		+			+	+	
Poikilocytosis					+	+	

I have to thank Dr. Julius Burnford, under whose care the patient was in the West London Hospital for the last months, and Dr. R. Elworthy for the blood examination.

Dr. E. STOLKIND (in discussion) said that this was the second case of erythro-leukæmia shown by him at the Clinical Section.[1] In British literature there were on record four other similar cases (Elliott, Hay and Evans, Myers, Muende and Parkes Weber).

[1] *Proc. Roy. Soc. Med.*, 1933, xxvii, 19.

Section of Anæsthetics

President—H. P. CRAMPTON, M.D.

[*December* 7, 1934]

DISCUSSION ON EVIPAN

Evipan as an Intravenous Anæsthetic

By R. JARMAN, L.R.C.P., M.R.C.S.

THE anæsthetic of choice several years ago was an inhalation one—chloroform, ether, or a combination of the two—but it was found that with these anæsthetics a large number of patients were upset by the induction period. The introduction of ethyl-chloride shortened this period and partially satisfied the patient, and it then became usual to attempt to make this phase as short as possible, continuing the anæsthetic with a mixture of chloroform and ether or warmed ether, various types of apparatus for administration being used. At the same time, the toxicity of these anæsthetics was fully realized and a means of reducing this was sought. Nitrous-oxide-and-oxygen was the only inhalation anæsthetic that did not produce toxic symptoms. Before sedatives in reasonably large doses were used, nitrous-oxide-and-oxygen was combined with warmed ether and this resulted in a first-class anæsthetic. The use of small amounts of ether produced a pleasant and quick induction and made surgical relaxation possible. But the problem of toxic symptoms, damaged lungs and emboli was still present.

It was then noticed that a smoother anæsthesia was obtained by using morphia in varying amounts in conjunction with nitrous-oxide-and-oxygen than by using oxygen alone. Paraldehyde and ether-olive-oil emulsion were then given per rectum, with still better results; in fact the emulsion was often used as the total anæsthetic. Ether was given intravenously, with varying measures of success.

Premedication.—At about this time the general public were beginning to demand to be put to sleep in their beds, or at least to be put into a state of somnolence that would render them unconscious of the transit from bed to anæsthetic room or theatre and would relieve them of the knowledge of having a mask on the face and of the feeling of suffocation as induction took place.

The advent of barbiturates.—The use of barbiturates gradually became accepted as a means of premedication. The first of these was somnifaine, but this had such severe toxic effects that it was gradually discarded, though it has a certain following even to-day.

From this arose basal anæsthesia, when sodium amytal, nembutal, pernocton, and di-dial came into being. These were all given intravenously, though, with the exception of pernocton, they could also be administered by the mouth. They were tried-out in large and small doses and as a complete anæsthetic, but owing to the fact that they were broken down so slowly in the human system and to the alarming toxic effects they produced, they are now only used as basal anæsthetics to be followed by nitrous-oxide-and-oxygen with or without ether.

The rectal route.—At the same time as these different barbiturates were being tried-out, avertin made its appearance, and this was given per rectum in much the same way as paraldehyde. At first it was tried as a total anæsthetic but the results were not good, owing to the toxic effects of large doses. Both these drugs form a very satisfactory basal anæsthetic and take a definite place in premedication.

The intravenous route.—It was soon realized that before long another barbiturate must be sought, without the profound lasting toxic effects produced by nembutal, pernocton, sodium amytal, and di-dial, when given in excessive doses, and also one that had a greater margin of safety.

In February 1933, Abel imported the first hundred ampoules of evipan into England, and in a few weeks we had used it in one hundred successful cases. The results of these were published in the *Lancet*, 1933 (ii), 18, since which date we have published a second article in the *Lancet*, 1934 (i), 510, on the completion of one thousand cases. Up to the present moment, I have given over 2,000 anæsthetics, using evipan as a basal or a complete anæsthetic, supplemented in certain cases with gas-and-oxygen, spinal anæsthesia, etc.

As evipan was a new drug, it was first necessary to find out exactly how much could be done with it and we set out with this end in view. We performed, with complete success, practically all the common operations in surgery, with no unpleasant results. There were, of course, tremors, slight embarrassments of respiration, etc., some patients reacting better than others, and in some cases the anæsthetic had to be supplemented by gas-and-oxygen and even occasionally by gas-and-oxygen and ether. There were several danger-signals, owing to the airways not being maintained, or the respirations being depressed by the combined use of evipan and nembutal. The latter point only proves again that it is unwise to mix two barbiturates.

Whilst this research was in progress, we enjoyed the help of the pathological departments of three of the hospitals where this drug was being tried-out. These departments went to great trouble to discover whether the drug upset the condition of the patient in any way, and also in what way it was excreted. The utmost care was taken of the patient, the blood-pressure being recorded throughout the operation and afterwards, and in this we were ably assisted by the medical students under our care as well as by the house officers. The sisters also did their part in keeping a minute record of anything unusual that occurred.

Out-patients and in-patients.—We use evipan for operations in two distinct types of cases.

(1) Minor operations on out-patients : Anæsthesia for minor operations in the out-patients department is required only for a moment or two. No premedication is necessary or desirable, and only the minimum dose of evipan should be used. There is no need to withhold food or to wait until three or four hours have elapsed since the last meal. The dose of evipan is injected intravenously and is from 2·5 to 5 c.c. The operations commonly performed under this minimum dose are dental extractions, the opening of abscesses, whitlows, etc., the removal of nails and of specimens for biopsy, and similar procedures, requiring from thirty seconds' to a few minutes' anæsthesia. The operation should be commenced immediately unconsciousness is induced and, as with major operations under evipan, we have everything absolutely ready before the injection is begun. If no more than the minimum dose is injected, the patient is conscious again within two or three minutes ; he is allowed to rest on a couch or chair for from twenty to thirty minutes, and is then quite able to go home, preferably with attendance. If more than the minimum dose, however, has been injected, a longer period must be allowed for recovery, and a friend will be required to see him safely home.

We inject the first 2·5 or 3 c.c. fairly quickly (five to 10 seconds), and then allow a pause of about thirty seconds (which is the normal time for the complete circulation of the blood). At the end of this time consciousness is usually lost. If not, a further 2 to 3 c.c. is injected, and the minor operation is performed. The patient regains consciousness almost as quickly as he went under.

If the injection is steadily continued after the first 2 or 3 c.c. without any pause, a further 3 or 4 c.c. will have been injected before unconsciousness supervenes ; which means that the patient gets double, or more than double, the minimum dose ; unconsciousness lasts for from ten to twenty minutes ; a longer time is needed in the recumbent position for recovery, and the patient is more apt to show symptoms of drunkenness, and for a longer period, than if a smaller dose had been used.

(2) Operations on in-patients: Premedication is given for all minor and major operations upon in-patients. Our aims are: complete oblivion—or, at any rate, somnolence—while in bed, so that the patient may have no psychic shock, complete, or almost complete, unconsciousness of any preparation before the operation, and a peaceful sleep for some hours afterwards.

In order to ensure successful surgery under evipan it is imperative that suitable premedication is given. We have found the best and most reliable to be the Hoffmann la Roche preparation containing omnopon gr. $\frac{2}{3}$ and scopolamine gr. $\frac{1}{150}$, for all patients between the ages of 16 and 70. Half this dose may be given to a large child or older person. La Roche's ampoule contains the lævo-rotatory scopolamine, which is the sedative alkaloid of hyoscine, and does not contain the stimulating dextro-rotatory alkaloid.

The injection is given one hour before the operation and the patient is left quietly in a darkened room, or with a bandage round the eyes, in order to encourage sleep. Most patients are brought to the operating-table without being conscious that they have left their beds. If, however, as often happens, the patient insists on being guaranteed complete oblivion in the bedroom, the injection of evipan may be given one hour after the premedication, with the patient still in bed. He is then transported to the operating-table, and for all but short operations a second injection of evipan or another general anæsthetic is necessary.

Condition of the patient.—We make a careful investigation of all patients who are to undergo a major surgical operation. This includes a blood and urine analysis, in addition to a general clinical examination. We pay special attention to the blood-pressure and the Moots-McKesson cardiac-energy index. No enematization or purging, or any other form of dehydration, takes place at less than forty-eight hours before any major operation. The patient is supplied with plenty of fluids and glucose, and everything is done to ensure that his general condition is as perfect as possible under the pathological circumstances.

Contra-indications.—Liver: Evipan is metabolized in the liver very rapidly, and any gross hepatic disease, or the presence of jaundice, is a definite contra-indication.

Low blood-pressure: General feebleness of the patient and low blood-pressure, or a low Moots-McKesson ratio, contra-indicate the use of a drug which causes a definite, though temporary, fall in the blood-pressure.

Posture: We feel that the upright position, except perhaps in young healthy subjects, is a contra-indication to the use of evipan, because of the sudden fall in blood-pressure caused by this drug. We therefore advise that dental extractions should always be carried out in the recumbent, and not in the upright, posture.

Space: Lack of available space applies only to institutions where large numbers of patients are to be dealt with and where enough room is not available to allow all of them to recover sufficiently to be able to go home.

Other barbiturates: We do not advise giving evipan to patients who have already had other barbiturates as their premedication. Slow recovery and prolonged depression of respiration and blood-pressure have occurred only in cases in which nembutal was used for this purpose. We do not include any barbiturates in our premedication. Nevertheless, in operating on children we have frequently given nembutal, gr. $1\frac{1}{2}$, followed one hour later by a full dose of evipan administered intravenously, without any untoward effect.

Technique.—For minor operations upon in-patients a full dose (1·0 g. dissolved in 10·5 c.c. sterile water) may be given without premedication, or combined with omnopon and scopolamine one hour before. For major operations evipan may be used either as a total anæsthetic or as a basal anæsthetic.

As a *total anæsthetic* we use evipan, combined with omnopon and scopolamine as premedication. The full dose may be repeated as often as required during the operation. For a strong healthy young adult we have often found it necessary to

repeat the full dose within a few minutes, but in younger or older patients the repetition is seldom required under from twenty to thirty minutes. The maximum number of times that we have found it necessary to repeat the injection has been four times over a period of two hours.

Evipan may be used as a basal anæsthetic, again preferably with omnopon and scopolamine as premedication. This is given in order that the patient may be unconscious of being moved from his bed, or of having a spinal anæsthetic, or of the passage of an endotracheal tube. If further injections of evipan are not given, and if an inhalation anæsthetic is required, we give nothing but nitrous-oxide-and-oxygen, and we have always avoided the use of either chloroform or ether, which drugs are not only dangerous in themselves, but are notoriously more dangerous in combination with barbiturates.

For example, for such operations as gastrectomy, cholecystectomy, hysterectomy, or rectectomy, we frequently use evipan after the premedication, then administer a spinal anæsthetic, and later, in order to maintain unconsciousness throughout the whole period of operation, either repeat the dose of evipan, or continue anæsthesia with nitrous-oxide-and-oxygen, by means of the McKesson apparatus. Where a closure of the upper air-passages is likely, we produce anæsthesia with evipan, then pass the intratracheal tube transnasally and continue anæsthesia—if, and when, necessary—with more evipan or with nitrous-oxide-and-oxygen.

Dangers.—The jaw: In from fifteen to twenty-five seconds the patient is entirely unconscious, and the first phenomenon noticed is dropping of the jaw. This requires careful and instantaneous adjustment. An attendant should always be present to see that the jaw is not allowed to fall back, and to maintain an adequate airway. Dropping of the jaw may be partly avoided by the patient's head being to one side. The jaw is more easily supported if the patient has a small dental prop between the teeth. The airway is always completely maintained if a rubber (Phillips') airway is inserted into the pharynx immediately unconsciousness takes place. The danger of allowing the jaw to relax and the tongue to drop back, thereby causing obstruction of the air-passages, is a very serious one, therefore it will be seen that evipan should never be administered single-handed, except in the most unusual circumstances.

Blood-pressure: There is always a fall of 20%, or even more, in the blood-pressure. In our experience it has had no deleterious effects or after-effects, but we do not use evipan for patients with a low blood-pressure. To do so is to ask for trouble, especially if old and feeble persons are anæsthetized in the sitting posture.

Respiration: There is a similar depression of respiration, but this, again, is very transient and, provided the airway is maintained, no harm occurs.

Restlessness, twitchings: Occasionally slight involuntary movements and general tremors are seen. These are never gross, but they are a little disconcerting to the beginner working with evipan. They very seldom happen if our premedication has been given one hour beforehand, and are readily overcome by giving a further injection of from 5 to 10 c.c. of evipan.

Signs of drunkenness: Patients who have been given more than the minimum dose, and who are allowed to go home when they are apparently recovered, have been known to exhibit signs of drunkenness in the street. If more than 3 c.c. have been given, ample time must be allowed for recovery to take place, and a comrade should see the patient home.

Advantages.—Our standard anæsthetic is still nitrous-oxide-and-oxygen, given with a McKesson apparatus, without the use of ether or chloroform, and preceded by omnopon and scopolamine premedication, but although the majority of our patients are treated in this way, we are using intravenous evipan for an increasing proportion of our work. Where it is essential that no drop in blood-pressure should occur, nitrous-oxide-and-oxygen is the general anæsthetic of choice; similarly, it is so

when instantaneous recovery is desirable. Both forms of anæsthesia allow full premedication and prevent psychic shock; they are not followed by vomiting, and do not aggravate any pathological condition that may be present.

Cases of already established pulmonary disease are, we hold, better treated without any form of inhalation anæsthesia, and for many of these evipan has proved ideal.

We feel that until many thousands of cases have been operated upon under evipan, it is strongly advisable always to have at hand a positive-pressure apparatus for the administration of carbon-dioxide-and-oxygen, or nitrous-oxide-and-oxygen. We therefore do not operate under evipan by itself without a McKesson apparatus at hand.

Antidotes.—The antidotes for evipan do not differ from those for any other form of general anæsthetic, nor are they more often needed. For collapse, coramine is by far the most reliable drug, but it must be used liberally; 5 c.c. should be the average dose, and 10 c.c. may be given quite readily for any general collapse. For purely respiratory failure from whatever cause, alpha-lobeline produces direct stimulation. Three-twentieths of a grain, or even twice that amount may be given intravenously for rapid action, or subcutaneously for slow action. The other direct respiratory stimulant is a gas given by mouth, if possible under pressure, consisting of $7\frac{1}{2}\%$ carbon dioxide with oxygen. A cylinder of this mixture in these proportions should be in every operation room and every recovery room. Lately we have been trying the effect of icoral and picro-toxin, which appear to be even more potent general stimulants than coramine.

Midwifery.—Up to the present moment a large number of Cæsarean sections have been performed in all parts of the country under evipan alone and, from all accounts, these have been completely successful. During twenty minutes of perfect surgical anæsthesia the baby has been removed from the uterus and the abdominal wound closed up, with no unpleasantness or anxiety on the part of either surgeon or anæsthetist.

With regard to straightforward labour, I have not used evipan myself, but several general practitioners have used it in small doses for the second and third stages. That is to say, 2 or 3 c.c. have been administered before the expulsion of the head and if this has not been sufficient, it has been followed by a further 2 c.c. The largest dose that has been given in any of these cases has been 8 c.c. in all, and the results that these various doctors have described to me have been all that could have been expected of evipan, which has given rise to no anxiety whatever, either during the course of labour or for some time afterwards. In no case, either of Cæsarean section or of straightforward labour, has the child suffered in the slightest degree. In spite of all this, however, much work has still to be done before it can be positively stated that evipan is of true value to the average general practitioner in ordinary cases of labour.

After-effects.—We have had no deaths following the use of evipan in over 2,000 cases. Careless nursing and failure to maintain an airway when the patient was returned to bed gave us a few minutes' anxiety in a few cases in our earlier experience. No pathological process appears to have been aggravated. Restlessness has been very marked in some dozen patients, all of them very highly strung. A definite, though very small, proportion of patients are found to vomit after the use of any opium derivative and we consider that the very small proportion, about 1%, of patients who have vomited after evipan is not greater than the proportion of those who vomit after the use of an opiate alone. No patient who has had evipan alone —i.e. without premedication—has vomited.

No harmful effects were noticed if a little leakage occurred around the vein and the resultant shock from evipan was negligible.

It is of interest to note that there have been in the region of 90,000 administrations of evipan in this country since the introduction of the drug in March 1933, and

out of this total only 16 deaths took place when evipan was used and, according to the post-mortem reports, and to the coroner's findings, not one of these fatalities was attributed to evipan anæsthesia. This in itself goes far to prove that in experienced hands evipan is a very valuable addition to the anæsthetist's armamentarium.

Conclusions.—Provided evipan is not administered single-handed, or to patients in the upright position, or to old and feeble subjects, and provided that an adequate airway is maintained, we are of opinion that this drug has a very large scope in the field of safe and useful anæsthesia.

Evipan in Dental Anæsthesia

By R. R. Macintosh, F.R.C.S.Ed.

To begin with, I shall refer to operations for simple extractions, of which hundreds are carried out in London every day. The great majority of these cases present few difficulties to the anæsthetist, but it is not sufficiently realized, outside the dental profession, that in a small percentage of them the problem of anæsthesia is by no means so simple. This applies particularly to two totally different types of patient. The first is the robust individual, often alcoholic, who boasts of his destructive achievements under previous anæsthetics. Even to an experienced anæsthetist, the provision of five minutes' tranquil operating-time for these cases is not an easy one, and is often achieved only by pushing the patient to a degree of cyanosis which might be dangerous if carried any further. Before an operation in a nursing-home this type of man can be subdued by morphia or other potent sedatives. In dental practice, however, this is impossible, because the patient is expected to be in a fit condition to go home immediately after his operation.

The second type of patient presents no technical difficulties at all. I refer to those who have a horror of inhalation anæsthesia. Although anæsthetized with ease by gas-and-oxygen, these people suffer mental distress both before and after the administration. You are all familiar with the patient who tells you that he dreads the anæsthetic far more than the operation. That this is a genuine fear of inhalation anæsthesia, in no way associated with the severity of the operation, is borne out by the fact that the same dread often exists in patients before dental extractions and other minor operations. In many cases this fear occurs in healthy subjects, and its cause is frequently traced to previous anæsthetics which may or may not have been administered badly.

The same fear is found also in psychoneurotics, and others in poor health. These patients, on waking up after a short gas anæsthetic, say that they feel that they have been asleep for anything from a week to an eternity; they remain bewildered for some time; often they have experienced nightmares. We should endeavour to protect them against a repetition of these ordeals.

As an example of the extreme opposite, I would quote the case of a well-known professor who, immediately after his anæsthetic, resumed his conversation with me exactly at the point at which it had been left off.

In my experience, about 90% of the usual operations performed in dental surgeries are accomplished successfully under gas-and-oxygen, with little inconvenience to patient, dentist, or anæsthetist. For the remainder, evipan fills a much-needed want. In the alcoholic it eliminates struggling and its attendant dangers; in the neurotic it mitigates greatly the unpleasant mental disturbance of which I have just spoken.

The great majority of patients, after a small dose of evipan, wake up and do not realize that the operation is over, or even that they have been asleep. Often their first remark is: "Don't begin yet, I am not yet asleep!" As an example of the lack of appreciation of lapse of time, I have in mind the case of a child, aged 8, whom

I anæsthetized for tonsillectomy. An injection of evipan in bed was followed by intratracheal gas-and-oxygen in the theatre. Half an hour later, the child's first question to the mother at the bedside was: "Are they still pricking me?" Remarks such as this are proof of the fact that the patient has suffered no distress.

It is a well-known fact that, those who have to face a series of inhalation anæsthetics, instead of being reassured by experience, dread each approaching anæsthetic more than the last, even when the administration has been in skilful hands. This apprehension has been almost entirely removed by the use of basal anæsthetics of which only evipan, owing to its rapid elimination, is suitable for use in dental surgery. I once had to anæsthetize a woman whose teeth were to be extracted in five sittings. She was very apprehensive on the first occasion, but was completely reassured by her experience with evipan, and she regarded the subsequent anæsthetics with equanimity.

It has been stated that evipan should not be given to a patient sitting upright, for fear of a fall in blood-pressure. This is too wide a generalization. Naturally, fall in blood-pressure depends on the amount of evipan which is administered, and on the general condition of the patient. It might be courting trouble to give sufficient evipan to keep a patient anæsthetized for fifteen minutes in the upright position, but enough can be given—and with complete safety—to keep him asleep for from one to three minutes, which allows plenty of time for quite a large percentage of extractions.

Apart from hospital work, my two partners and I have, to date, given evipan, either as the sole anæsthetic or as a basal anæsthetic, in over 1,000 cases in private practice, and more than half of these have been for dental operations. If the patient has been in average health, we have had no compunction about giving him evipan in the upright position, and we have had no cause to regret having done so. Among my patients are included colleagues who, already familiar with evipan technique in the dental chair, have chosen to be anæsthetized in this position.

It is of the utmost importance to maintain a free airway during evipan anæsthesia. For dental work, unless an intratracheal tube is passed, it is easier to do this with the patient upright than when he is lying down. In the supine position, the tongue, throat-pack, blood, mucus, and débris, gravitate downwards, and tend to impede free respiration.

For the majority of patients for whom I consider that evipan is indicated, I use the drug as a pre-anæsthetic and not as the sole anæsthetic. It is my practice to give just enough to produce sleep and then to continue with nasal nitrous-oxide-and-oxygen until the operation is finished. By following this technique a pleasant induction is assured and, owing to the small quantity of evipan used, recovery is reduced to a period of only a few minutes.

For dental work it is advisable to have the mouth gagged open before the injection. The masseter muscle does not relax under small doses of evipan, so that, in the case of a short dental operation, if a prop is not inserted, valuable time will be lost owing to difficulty in opening the mouth. Moreover, the use of force in opening the mouth may damage the teeth or gums and will certainly lighten the anæsthesia.

If evipan is to be used as a sole anæsthetic, one must endeavour to judge the length of an operation accurately. The difficulty of a particular extraction might be greatly overestimated—as in the case of a colleague who asked to be anæsthetized with evipan only: It was estimated that a particular tooth would take seven or eight minutes to extract, and 8 c.c. were given; the tooth, however, was out in a minute and the dose might have been halved.

In contrast to anæsthesia under nitrous-oxide and ether, the depth under evipan is uneven, being at its maximum almost immediately after the injection, after which, owing to the rapid elimination of the drug, it becomes progressively lighter. Dentists who have both extractions and fillings to do at one sitting may take advantage of

this fact. The extractions, being more painful, should be carried out in the early stage of deep anæsthesia, the conservative work being done while the effect of the anæsthetic is gradually diminishing.

Out of nearly a thousand cases I have met with two patients who, on recovering consciousness, became quarrelsome for from fifteen to twenty minutes. Both were men of naturally aggressive temperament. While the period of anæsthesia afforded by evipan was perfectly tranquil, the post-operative period was turbulent. Both patients required forcible restraint. Occasionally, following evipan, a mild degree of hysteria, lasting for a few minutes, is seen in women, and though rare, this occurrence is perhaps more frequent than after nitrous-oxide.

There are no unpleasant sensations during induction. Doctors and dentists whom I have anæsthetized with evipan have told me that they prefer it to any other anæsthetic that they have had, and I, personally, would choose to be anæsthetized with evipan rather than by any other method, but I would select my anæsthetist with care. When evipan was first introduced, I thought that the simplicity of the technique would narrow the scope of the expert anæsthetist. I am now of the opinion that its use should be restricted to those who have a sound knowledge of drugs and general anæsthetic routine. The simplicity of the procedure should not tempt the operator to give his own anæsthetics. The safeguarding of an unconscious patient is a whole-time job.

The general practitioner who gives gas until the patient is blue in the face, and then walks away from the chair, leaving the dentist to do his best, is finding his counterpart in the doctor who administers evipan, and then walks away from the field of operation, leaving the patient to look after himself.

Whilst attending operations, general practitioners have been impressed by the potentialities of the barbiturates given intravenously. One practitioner, after seeing pernocton used once, returned home, and some weeks afterwards I received a letter from him. He informed me that he had used pernocton successfully in ten cases, but his eleventh patient had nearly died. What had he done wrong? I replied that he had not been justified in using such a powerful drug with so little experience of it. Had this patient died, the blame would have been attributed, in some quarters, to the drug, and not to the incompetence of the doctor.

The relative safety of various anæsthetics is often discussed by doctors and dentists. It is frequently stated that gas is safer than ether, and that ether is safer than evipan. This statement appears reasonable, but it is not free from fallacy. In this country we regard gas as a safe anæsthetic, only because we do not ask much of it. It is my belief that if a cholecystectomy were attempted in the case of a powerful man under gas-and-oxygen only, more risk would be run than if he were guided through anæsthesia under a combination of gas, oxygen, and one of the more potent anæsthetics.

Similarly, if five minutes' peaceful anæsthesia in the dental chair is wanted for an extraction in the case of an alcoholic man, this can be obtained with less risk by means of evipan than by gas only.

Emphasis should be laid on the fact that in dental work evipan is indicated in cases presenting anæsthetic difficulty, and not difficulty in extractions. For example, it is of value for the fat bronchitic or alcoholic, in whom extractions are going to last only one or two minutes, but not for lengthy extractions in normal subjects.

Evipan is particularly suitable for administration in a private house where the anæsthetist is unable to wait after the operation. With evipan recovery is rapid, whereas after avertin, pernocton, chloroform, or ether, recovery may be protracted, and the patient is unfit to be left without skilled attendance.

I have been impressed by a fact to which, as far as I know, attention has not yet been drawn, namely that, as the result of a moderate dose of evipan, such as 6 c.c., the patient experiences sleep so deep and refreshing that his capacity for

further sleep is markedly diminished for several hours. In fact, when evipan is administered in the evening, a sleepless night may follow, unless a sedative such as omnopon, aspirin or medinal is given.

One is confronted with similar problems in choosing a basal anæsthetic for both major dental operations (e.g. excision of cysts, and the removal of impacted wisdom teeth) and other surgical operations. For these cases I prefer pernocton, which induces slumber of any desired depth, and of much greater duration than that induced by evipan. The main advantages of pernocton are:—

(1) The patient can be put into a light sleep in bed. If necessary, this can be done an hour, or even two hours, before the operation, in order to eliminate the panic which, in some cases, is experienced as the hour of operation approaches.

(2) When the patient comes round from the anæsthetic he remains under the influence of pernocton for some time. Owing to the well-marked amnesia which this drug produces, he recollects little of the hours following the operation. If he has been sick he remembers nothing about it. Complaints of after-pain are much less frequent than in patients who have had evipan or no basal anæsthetic at all.

For suitable cases, and in proper hands, I think the barbiturates, including evipan, are excellent, but I would temper my enthusiasm with a warning and say that they should be administered only by those who have had both considerable experience in the practical administration of anæsthetics, and opportunities for observing the effect of drugs on different types of patient.

Dr. W. Alexander Low: I have taken a series of 140 cases including, as far as possible, all types of operation, using a fixed dosage of 10 c.c. of evipan except in the case of children. No premedication is used except atropine gr. $\frac{1}{75}$ half an hour before operation. These cases cover all ages, from 9 years (a child who had an abscess of the shoulder opened under anæsthesia with $3\frac{1}{2}$ c.c. of evipan alone), to 77 (a feeble man, who had his mandible excised, under 10 c.c. of evipan with gas-and-oxygen, given through an endotracheal tube). One word in regard to the use of atropine. You have heard that Dr. Jarman does not like its use prior to evipan. My reason for giving it as a routine is that it dries up the secretion of saliva. This prevents a very troublesome cough, which occasionally arises when atropine is not given. The cough, in turn, sets up a spasm of the cords, and I have had two cases in which it lasted for about five minutes, and was very troublesome. I did not undertake this series with the idea of using evipan alone. Instead I wanted to see in what type of case evipan could be used (without other drugs), and again what type of case required the addition of gas-and-oxygen, and even gas-oxygen and ether or chloroform. Out of 140 cases 30 operations were successfully performed under evipan alone. These were minor cases, such as dilatation and curetting, cystoscopy, removal of polypi (nasal and rectal), and the opening of abscesses—cases in fact, in which gas-and-oxygen would almost suffice. The after-results were excellent; no sickness; no headache; the patient in many cases was able to take a meal and enjoy it a few hours after the operation.

I never had any anxious moments with any of these cases. The patients themselves were pleased and relieved that they had not had to submit to having a mask over the face.

The next group is evipan and gas-and-oxygen. There were 75 cases of this combination, that is, over half the total number. The operations performed included operation for hernia, operation for internal cartilage of the knee, breast operations, suprapubic cystostomies, setting of fractures, and most of the gynæcological operations, excluding the abdominal cases. Some abdominal operations can be performed when the patient is under evipan and gas-and-oxygen, but in my experience relaxation is not consistently good. Ear, nose, and throat operations—such as tonsillectomy, using an endotracheal tube—mastoids, intranasal antrotomies, and operation on the nasal septum are included. The addition of gas-and-oxygen widens the scope

tremendously, and also has the great advantage of lengthening the time the patient can be kept under. The amount of gas used in proportion to oxygen was lower, in most cases, than in ordinary gas-and-oxygen administration. The after-results were good: no headache; no sickness, except in three cases—a mastoid case in which the patient had been vomiting before operation, a tonsillectomy, and a dental extraction; in the two latter cases I think that blood was swallowed.

The next group is evipan, gas-oxygen and ether, of which there were twenty cases. Under this combination operations requiring relaxation were performed, such as abdominal section. It required very little ether indeed; in fact often only a whiff now and again was necessary to produce relaxation. In most cases the patients were unaware they had had ether. They did not vomit and could not even taste the ether. The general condition after operation was good, but there is one point against this combination, when used for large major operations with much post-operative pain. The patient wakes to the pain too soon. This is a decided disadvantage, and in choosing the anæsthetic in such cases, avertin, for instance, would be more suitable.

The next group is evipan, gas-oxygen and chloroform. This group is largely experimental. I wished to see if chloroform had any advantages over ether, as an adjunct to evipan and gas-and-oxygen. Very little was required to produce relaxation. I found that neither during the operation nor after did the result show any advantage over ether. Chloroform is a depressant—the blood-pressure has already been lowered by evipan. It must follow that the risk of using evipan, gas-oxygen and chloroform is greater than that of using evipan, gas-oxygen and ether. Under these circumstances I do not advocate the addition of chloroform to evipan and gas-and-oxygen.

I gave a few regional anæsthetics for colostomies, and a few low-spinals for rectal operations, and in these cases have used a small dose of evipan to send the patient to sleep during the operation. This has been perfectly successful, but I am opposed to using evipan with high-spinal anæsthesia, as the combined fall of blood-pressure from each makes it dangerous. The question was raised a short time ago at an anæsthetists' meeting, as to whether evipan affected the child when used in induction of labour. I gave 10 c.c. of evipan in several cases of induction—a few unsupported by gas-and-oxygen, and the rest with its addition. The results have been good, and it appeared to have no effect whatever on the baby. Labour commenced and was terminated in three of these cases within the twenty-four hours.

I have come to the following conclusions with regard to evipan:—

(1) The technique of preparing the syringe and injection of evipan should be strictly followed.

(2) Evipan is a safe anæsthetic, provided that it is used by someone accustomed to all types of anæsthesia.

(3) When evipan is used alone it is only suitable for minor surgical cases.

(4) It can be safely combined with other anæsthetics such as gas-and-oxygen and ether, regional and low-spinal anæsthesia, but chloroform and high-spinal anæsthesia should not be combined with evipan.

(5) Sickness and headache are practically abolished, even when evipan is used in combination with gas-and-oxygen or gas-oxygen and ether—the amount of ether used being very small.

(6) It is the wrong type of anæsthetic even when combined with gas-oxygen and ether to use in abdominal cases or in major surgery, because the patient regains consciousness almost as soon as the operation is at an end.

(7) Explicit instructions should be given to the nurses in charge of the case. Firstly, in regard to morphia after operation: Morphia, gr. $\frac{1}{8}$ can be given as soon as the patient is restless and complains of pain. If this dose is not sufficient, it can be repeated. A larger dose of morphia is dangerous, as the patient may collapse, and

once given, the drug cannot be recovered. Secondly, they should be warned what might happen should a patient collapse, and should know how to deal with it. Lobeline should be given for respiratory failure, intramuscularly or intravenously according to the urgency. Carbon-dioxide should be given if respiration has become too slow. It is waste of time to give 5% or 7% carbon-dioxide and oxygen. Give carbon-dioxide until the patient begins to take deep inspirations, then stop it. There is plenty of oxygen in the air, and the carbon-dioxide can be repeated as often as is necessary. Coramine should be given if a cardiac stimulant is required, and it also can be repeated as often as required.

(8) Its main disadvantage is the restlessness after operation; this occurs in only a small percentage of cases and can be controlled by a small dose of morphia. Twitching immediately the drug is injected can be almost abolished if the drug is injected very slowly. By that I mean: Take forty-five seconds to inject the first 3 c.c.—wait thirty seconds, then inject the remainder at 1 c.c. per ten seconds. If any sign of twitching still occurs, wait and inject more slowly. Another disadvantage which occasionally occurs is the absence of veins suitable for intravenous injections.

With regard to the teaching of evipan administration to students: I am in favour of showing students how evipan is given, paying particular attention to the technique, and explaining the dangers and how to combat them. I cannot help feeling that evipan or a drug of this type, given intravenously, is going to take its place in anæsthesia of the future, either used alone or in combination with gas-and-oxygen. It is therefore important that the student of to-day should be conversant with the methods employed. The accidents which have occurred were probably due to lack of sufficient experience in the use of the drug. A student is only required to give twenty anæsthetics to be signed-up before being qualified. After giving only so few anæsthetics he cannot expect to be fully conversant, either with anæsthesia in general, or with evipan in particular. When students are qualified it will fall to the lot of many to give anæsthetics whilst holding house appointments. This brings us to an important point. Should house-officers be allowed to administer evipan? My answer to this is that they should not be allowed to do so until they are expert in the giving of ordinary general anæsthetics. When they go out into practice a number will give their own anæsthetics. Some of their patients will ask for evipan or an anæsthetic of that type. If they know something about the administration, they will be more competent to give it, if they wish to do so, and—probably more important still—they will realize its limitations and their own.

My next point is the attitude of some of our colleagues towards these new anæsthetics. An anæsthetist is called in, and it is sometimes intimated to him that he is not to use any of these "new-fashioned drugs." Anæsthetists all welcome the co-operation of the surgeon or physician in the case and they are only too pleased to discuss with them the anæsthetic to be used. But surely it should rest with the anæsthetist to decide what anæsthetic will best meet the needs of the patient and the surgeon! I should like to stress this point, as it is important. We do not combine enough. A short conversation on the telephone is quite sufficient in most cases to produce satisfaction on both sides. It is sometimes found that this hostile attitude towards a drug has been adopted solely because of one reported accident, and not because of any special knowledge that that particular individual has of the drug. I have met patients who have been told by their medical advisors that evipan is very dangerous. This is quite the wrong attitude to adopt unless supported by conclusive evidence. Evipan and its like were brought out for several reasons, but with one main object in view—to improve the condition of the patient before and after the operation. If nervous apprehension before operation, shock at the operation and the after-effects, such as headache, nausea and vomiting, can be avoided, the patient is materially helped on the road to a speedy recovery, and therefore the greater is the success of the operation.

Mr. I. W. Magill: The intravenous use of the barbiturates in this country was stimulated by the introduction of nembutal in 1930. It was of historic interest in the present discussion that in 1931 the *Lancet* ((i), 595), in a leading article prophesied that the barbiturates would not be in use in 1932. This prophecy was followed later by a leading article in the *British Medical Journal* (1932, (i), 438), which practically condemned the intravenous injection of these drugs. In spite of this attitude on the part of our leading medical journals, evipan was introduced. The popularity of evipan is proof of the efficacy and accuracy of dosage obtainable by intravenous injection, a method of which I have always been an advocate.

Evipan can be used in anæsthesia in two ways:—

(1) As a basal hypnotic it is effective, as far as induction of subsequent anæsthesia is concerned, but its transient qualities render it inferior to other agents when the help of the basal hypnotic is required, (*a*) during maintenance or (*b*) to promote post-operative sleep.

(2) As a complete anæsthetic it is clearly of inestimable value in many short operations, such as dental extraction in patients who have proved difficult under nitrous-oxide, or for the insertion of radium needles, etc. But the use of evipan in long dental operations or in major surgery is quite a different proposition.

The maintenance of the airway is of first importance. In long dental operations it is generally agreed that intubation alone guarantees this safeguard. If intubation is to be carried out, evipan as the sole anæsthetic is unsatisfactory. The use of evipan alone in operations—such as tonsillectomy or appendicectomy on patients in whom there is no contra-indication to the use of other forms of general or local anæsthesia, appears to me unjustifiable.

The method of administration of evipan calls for careful consideration. The injection of a predetermined dose based on body-weight is as unreasonable as an attempt to obtain surgical anæsthesia by drinking a calculated dose of chloroform. The barbiturates are notorious for the variation and duration of their effects, and evipan is not an exception. I have obtained anæsthesia of twenty minutes' duration with 2·5 c.c. in a man; and with 9 c.c. I have failed to obtain satisfactory anæsthesia for bronchoscopy in a boy aged 9. This latter patient slept for twelve hours and was drowsy for twenty-four hours following the injection.

Evipan should be regarded as one member of a group of drugs which is capable of infinite expansion. I have suggested to one maker the need for a barbiturate as efficacious as evipan, but with a longer action. I believe that this new derivative will be forthcoming in the near future. In the meantime evipan must be regarded as having a definite place in anæsthesia.